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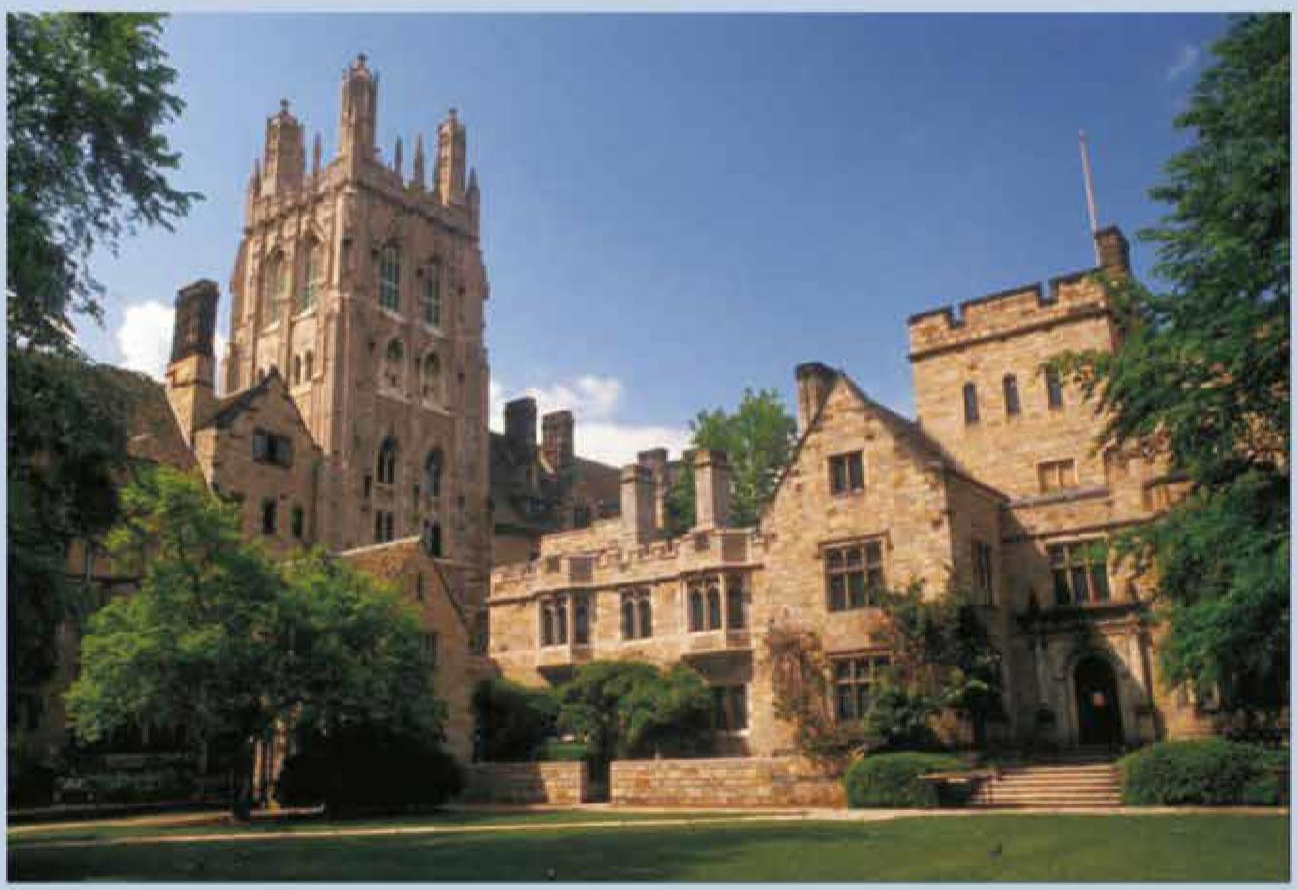

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PROTEFLAZID®: specific activity against Herpes virus in preclinical investigations and its efficacy/safety in clinical practice (systematic review)

Annotation: It was shown specific antiherpes activity of medicin Proteflazid® in preclinical stage of investigations. It was proved that Proteflazid® has polyphar-macologic activity: blocks DNA-polymerase and thymidine kinase in Herpes virus infected cells, induces synthesis of endogenous α- and γ-interferones, has antioxidant activity, and renders apoptose modulative effect. It was confirmed in clinical conditions ethiopathogenetic efficacy of antivirus medication Proteflazid® (drops) for Herpes virus infection. It was demonstrated safety and therapeutic efficacy of Proteflazid® (drops) in more than 3200 patients (adults, children, pregnant women). Continuous monodirec- tion of therapeutic efficacy of medication was observed in 65 investigations during pe- riod since 2000 till 2015.

Keywords: Proteflazid®, antivirus efficacy, Herpes virus infection, prophylaxis, treatment.

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PROTEFLAZID®: specific activity against Herpes virus in preclinical investigations and its efficacy/safety in clinical practice (systematic review)

Annotation: It was shown specific antiherpes activity of Proteflazid® in preclinical stage of investigations. It was proved that Proteflazid® has polypharmacologic activity: blocks DNA-polymerase and thymidine kinase in Herpes virus infected cells, induces synthesis of endogenous a- and Y-interferons, has antioxidant activity, and renders apoptose modulative effect. It was confirmed in clinical conditions ethio- pathogenetic efficacy of antivirus medication Proteflazid® (drops) for Herpes virus infection. It was demonstrated safety and therapeutic efficacy of Proteflazid® (drops) in more than 3200 patients (adults, children, pregnant women). Continuous monodirection of therapeutic efficacy of medication was observed in 65 investigations during period since 2000 till 2015.

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Relevance. A herpes virus infection (HVI) is the common name of infectious diseases caused by structurally homogenous group of viruses belonging to the family *Herpesviridae* [1]. The family includes more than 100 representatives, of which for most pathogenic viruses for human include herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpes virus 6 type (HHV-6), human herpes virus type 7 (HHV-7), human herpes virus type 8 (HHV-8) [1, 2]. The common pathogenetic and biological properties of herpes viruses (hepatitis B) are intracellular parasitism, capacity for life-long persistence in the body, dependence of the infection process nature on virus carrier immunity status, tendency to recur. HV ability of long-term persistence causes the possibility of development in the human body of several forms of infection - acute, latent, and chronic recurrent, while a transition of one infection form to another is possible [2].

The numerous studies show that 65 to 90% of the world population is infected with one or more types of HBV [1, 2, 3]. HV infection in human is accompanied by clinical symptoms of an acute infectious disease on average in no more than 50% of people. In the remaining patients the infection is asymptomatic, that is especially true for teenagers and adults. But, in spite of the initial clinical manifestations silence of latent HVI, the viruses even in inactive, cell integrated state can cause chromosomal abnormalities in human genetic material and, thus, contribute to the development of carcinogenesis, autoimmune disorders, degenerative changes in tissues and organs. HVs are polytropic and during reactivation can attack virtually all organs and systems of the human body. The systemic nature of lesions cause the variety of clinical forms of HVI, the features of which depend not only on the above factors (virulence of the virus, state of immune system), but also on HV type [2].

HVI issue is the interdisciplinary one. Depending on the prevalent region or organ lesion, clinical form, age, sex the HVI patients can be screened and treated by pediatricians,

gynecologists, infectious disease specialists, dermatologists, neurologists, urologists, oncologists and other specialists. HVI therapy is complex and often multicomponent. This is due to the fact that currently there is no single drug and treatment regimen which would be sufficiently effective against HBVs and all pathological conditions they cause.

According to modern studies, as the causal treatment to suppress the propagation of HV the flavonoids can be used that have antiviral and immunocorrective actions. In 2000, the range of antiviral agents was expanded by the original drug Proteflazid® (drops) («SMC "Ecopharm", Ltd., Kyiv, Ukraine) with the antiviral, immunomodulatory and interferonogenic effects [4, 5], which has been of great practical importance, and was accompanied by a number of scientific studies to assess its efficacy and safety in the herpes viral pathology.

Proteflazid® is a liquid alcohol extract of wild cereals *Deshampsia caespitosa L.* and *Calamagrotis epigeios L.*, the main active ingredient of which are flavonoids like quercetin; the molecule base is formed of flavonic oxygen-containing heterocycle.

As it turned out, along with safety, Proteflazid® (drops) is therapeutically effective at any stage of infection (and not only at the time of replication), as opposed to the acyclic nucleosides. Furthermore, repeated and prolonged courses of drug administration did not lead to immunosuppression and refractoriness of immune system. The drug proved its efficacy, effect on the different types of HV and has demonstrated the ability to provide anti-relapse action [4, 6].

The complexity and lack of effectiveness of existing treatment of HV infection has become a prerequisite for the analysis of materials supporting the specific antiherpetic activity of Proteflazid® and pathogenic justification of choice, efficacy, and safety of the drug in treatment of HVI different clinical forms in both children and adults in the acute phase and during convalescence.

Objective: to analyze the scientific data and practical evidence confirming the efficacy and safety of a medicinal product Proteflazid® (drop) at the stage of pre-clinical study and clinical treatment of herpesvirus infections.

Materials and Methods: scientific publications, preclinical and clinical study reports, systematic analysis.

Results and discussion. In a systematic review the results were analyzed of preclinical and clinical studies of Proteflazid® (drops) in the scientific and medical institutions of Ukraine, Belarus, Russia, Uzbekistan, and Kazakhstan.

Evaluation of the specific antiherpetic activity of Proteflazid® at a stage of preclinical studies. Rybalko S.L. (2002), using Vero cell culture, showed pronounced antiherpethetical activity of Proteflazid® drug. *In vitro*, in the prophylactic and therapeutic effect of various drug concentrations (from 6.8 to 0.212 μg/ml) an inhibition of the reproduction of Herpes virus was observed by 3.0-6,0 lg TCD_{50} [7]. Deryabin P.G. (2013, Russia) using the same cell model (HSV-1 in Vero cell culture) confirmed that Proteflazid® significantly inhibits the cytopathic effect of HSV-1 in the prophylactic and therapeutic schemes in studied concentrations; selectivity index value was obtained (SI – selective index)> 100 [8].

In vivo the antiherpetic activity of Proteflazid® was demonstrated in models of herpes meningoencephalitis in mice, genital herpes in guinea pigs, and herpes keratitis in rabbits.

Performance Index (PI) of the drug preventive effect was 50.0; treatment index - 33.3. Proteflazid® at a concentration of 1.36 μg/ml in guinea pigs genital herpes model reduced symptoms, duration of the disease up to 9 days, caused a 60% therapeutic effect. Increasing the concentration to 6.8 μg/ml increased the therapeutic efficacy of the drug up to 95%. In herpetic keratitis model the treatment with Proteflazid® drug at a dose of 0.68 μg/ml completely prevents the development of herpetic keratitis in rabbits [7, 9].

The study of antiviral action of Proteflazid® by Rybalko S.L. (2002, 2010) demonstrated that the active drug substance is able to inhibit in infected cells the virus specific enzymes – thymidine kinase (TK) and DNA polymerase, resulting in reduced ability or complete blocking of viral replication. The system "brain cells – herpes virus type 1" when exposed to different concentrations of Proteflazid® demonstrated that the drug at a dose of 10 μg/ml inhibits the TK-activity by 30% at a dose of 25-50 μg/ml – 50%, at a dose of 75-100 μg/ml - 70%. DNA polymerase activity in the same system at a concentration of Proteflazid® drug up to 75-100 μg/ml was reduced from 20 to 28% [7, 11].

Since Proteflazid® is a multicomponent mixture of natural compounds, in order to determine the specific activity of the individual compounds, the biologically active drug substance of Proteflazid® (BADS) was isolated. BADS is represented as stable molecular complex compounds of flavonoid aglycones: tricine, apigenin, luteolin, quercetin, and rhamnazin as O and C- glycosides (included in a matrix of natural excipients). BADS chemical purity is 93.8%. Rybalko S.L. et al. (2010) conducted a study of the antiviral activity of BADS on continuous culture of VNK cells. The authors noted that BADS inhibits herpes virus reproduction in dilutions ranging from 1:40 to 1:1280 (concentration from 12 μg/ml to 0.37 μg/ml). The inhibition was demonstrated of the infectious titer of herpes virus by more than 4.5 lg ID_{50}. The values of BADS maximum tolerated concentration for VNK cells, was equal to 825 μg/ml, and minimum active concentration of BADS towards HSV2, equal to 0.37 μg/ml, allowed establishing the SI value of 2230, indicating a highly selective action on BADS on HSV2 [11].

Study of BADS antiherpetic activity in *in vivo* experiments was carried out on the herpes meningoencephalitis model in white mice caused by HSV1. It is shown that BADS protective effect at a dose of 0.48 mg/kg administered for prophylactic and therapeutic purposes, by IE and infectious titer in mouse brain tissue have equal in efficiency action to acyclovir at a dose of 10 mg/kg. Antiherpetic activity (HSV-2) was also studied on the model of genital herpes infections in guinea pigs. The study drugs (BADS and acyclovir in the form of ointment) were applied to scarified infected skin of guinea pigs 1 time per day for 5 days. Experiments have shown that BADS exhibits antiviral activity with a more pronounced therapeutic effect (therapeutic action index of 93.5%) vs acyclovir ointment (therapeutic action index of 56.0%) [11].

Thus, the pre-clinical studies have demonstrated the presence in Proteflazid® biologically active substances of high levels of SI and IE [7-12].

One of the mechanisms of antiviral action of Proteflazid® is interferonogenic activity. M.P. Zavelevich et al. (2002) indicate that the drug *in vitro* dose-dependently stimulates the production of interferon (IFN) in human leukocytes and in continuous culture of MDBK cells. Typing showed that the drug is an inducer of α- and y-IFN [13]. Studies have confirmed that Proteflazid® can induce interferon synthesis both *in vitro*, and *in vivo* only in 3 hours after administration [10-12].

In addition to the antiviral activity Proteflazid® exhibits antioxidant properties: increases the resistance of cells to free radical stress in infections, reduces the negative effects of drug chemotherapy, and helps the body to adapt to adverse environmental conditions. In *in vitro* experiments it was demonstrated that the drug inhibits 2-fold the free radical processes induced by hydrogen peroxide [10].

Proteflazid®, showing an apoptosis modulating activity promotes primary prevention of oncological diseases against the background of chronic (latent) viral infections. Active BDS through the activation of caspase 9 recovers the ability of cells infected with viruses, to apoptosis, reducing the activity of the mutated proliferative processes in cells [11].

In 2015 a systematic review was published on the effectiveness of Proteflazid® in Epstein-Barr virus infection in pre-clinical study and clinical practice (Grinevich A.I. et al., 2015). The review based on the publication of preclinical and clinical study results have proved the effectiveness of Proteflazid® for this species of herpes virus infection in children and adults [14].

Therapeutic efficacy and safety of Proteflazid® (drops) in various clinical variants of HVI in children and adults. Genital herpes (GH) is a serious medical and social problem. According to foreign researchers GH takes the 3rd place among the frequency of occurrence of the sexually transmitted diseases. In the majority of patients the course of GH against the background of immunological disorders shows chronic recurrent nature, dramatically reducing the quality of life of patients, increasing the risk of bacterial, neurological disorders, infertility. Repeated courses of chemotherapy with antiviral drugs do not guarantee the termination of GH relapses. The search for new drugs and improvement of existing treatment regimens are ongoing.

In 2000, Ventskovsky B.M. presented the results of a clinical study "Open-label study on tolerability and preliminary assessment of the efficacy of Proteflazid® (drops) in treatment of primary and recurrent infections caused by *Herpes genitalis*". It was established that Proteflazid® (drops) is highly effective in treatment of primary and recurrent GH and does not cause serious side effects, as compared to efficacy and tolerability of acyclovir [15].

Vovk I.B. et al. (2002) were among the first to publish data on Proteflazid® efficacy in gynecological practice. Their study involved women with chronic inflammatory genital viral and chlamydial infection. There was a significant improvement in the clinical presentation of the disease, normalization of main protective function factors of cervical mucus (sIgA, lysozyme and C_3 complement component), reducing contamination of the genital tract with pathogens [16].

Andriets O.A., et al. (2004, 2005) studied the role of GH in the development of inflammatory processes of genital organs and therapeutic features of these disorders in prepubertal and puberty girls. Proteflazid® was administered only to girls who had the HSV2 antigen detected in smears, as a course up to 4 weeks. It was found that after 1 week of dosing 40% of patients had significantly decreased clinical symptoms and complaints, after 2 weeks of treatment 85% of patients had rashes completely disappeared in the genital, as well as subjective sensations. In the course of therapy the increased levels were observed of IL-1β, IL-2, the TNF-α in the peripheral blood and IL-1β, slgA in vaginal secretion; this effect was maintained after the course of treatment, indicating the process of recovery and repair [17, 18].

In the same period Kishakevich I.T., Romashchenko O.V. et al. (2005) justified the expediency of prescription and confirmed the efficacy of Proteflazid® in treatment of inflammatory diseases of the genitals, including against the background of mixed infections. The similar positive data was obtained as a result of the studies. The prescription of drug was accompanied by positive changes on the part of local immunity – normalized levels of immunoglobulins, lysozyme in the cervical mucus, slgA levels increased significantly with a parallel decrease in the level of IgM, indicating activation of humoral immunity and reduced antigenic load, due to the reduction of genital infection. Some patients in the early days of the drug therapy had an exacerbation observed, which was quickly reverted. Positive dynamics was observed in more than 83.3% of patients. The incidence of relapses was reduced to 5.0% [19, 20].

In 2003-2005 Grinkevich T.M. conducted a series of studies on the efficacy of different therapy regimens in GH. It was shown that Proteflazid® eliminates the imbalance of cellular and humoral immunity, has a positive clinical effect, reduces the frequency of relapses by 19%, helps to normalize the vaginal microbiocenosis, and accelerates re-epithelialization in herpetic endocervicitis [21, 22].

Another author (Gopchuk O.M., 2006) developed comprehensive medical and preventive measures for the correction of neurohumoral menstrual disorders in patients with HVI based on Proteflazid® drug. He observed against the therapy background the normalization of the menstrual cycle, no detection of GH in specific studies and recovery of vagina microbiocoenosis [23]. Having continued the study Gerasimova T.V., Gopchuk O.M. in 2007 presented the results of the Proteflazid® use in the treatment of GH and human papillomavirus infection. Proteflazid® was administered in combination with Viferon. The duration of preventive treatment was 3-6 months. Clinical effectiveness of the proposed scheme of treatment was 82.8%, recurrence rate of herpes infection was 2-3 fold reduced, HPV - 1.5-2-fold [24].

Zapolskiy M.E. in publications of 2006 and 2012 presented data on clinical characteristics and therapeutic efficacy of Proteflazid® drug in patients with GH complicated with erythema multiforme exudative (magnetoelectric effect). It was noted that in cases of uncomplicated GH the positive dynamics during therapy was observed already on days 4-5 of treatment, complete disappearance of the manifestations – days 5-6. In case of magnetoelectric effect the epithelialization of erosions and bullous elements in 96.9% of patients of the main group resolved by day 9-10 of treatment. Repeated relapses of magnetoelectric effects were observed only in 12.5% of patients throughout the year. The immunological parameters showed the positive dynamics in relation to the basic elements of cellular immunity, reduced content of CIC [25, 26].

Similar studies have been carried out by other authors. Thus, Lesovoy V.N., Yakovleva E.V. (2006), Shymanskaya I.G. (2007, Belarus) assessed the Proteflazid® drug efficacy in treatment of patients with GH, including both symptomatic and asymptomatic forms. It was noted that 95% of patients receiving the drug experienced positive clinical outcome; 28.1% of patients reported a reduction of activity and duration of clinical manifestations of relapse [27, 28].

According to Ayzyatulov R.F. (2008), the Proteflazid® use in treatment of mixed urogenital infections in women, a positive clinical dynamics was observed already on day 3-5

of therapy; termination of discharges – day 6-8, in most patients the elimination of pathogen was recorded [29].

Flax G.A. (2008, Russia) confirmed the high efficacy of Proteflazid® in patients with HVI, as a decrease in the frequency of exacerbations, normalization of laboratory parameters (the disappearance of the virus in PCR smears, reduction and/or disappearance of antibody titer with ELISA) during the acute manifestations of GH and, especially during remission [30].

Popova T.V. (2008) studied the features of differentiated treatment regimens in women (including HIV infection) with inflammatory diseases of the cervix. 68 HIV-infected women had Proteflazid® (oral and topical) prescribed in the complex of prolonged therapy. It was found that the overall efficiency of the course of therapy is 93.8%, in most patients the stabile regression was observed of the inflammation symptoms, normalization of the vaginal microflora [31].

At the same time, the researchers Sundukov A.V. et al. (2008, Russia) conducted a clinical trial of Proteflazid® drug in treatment of some HVI in adults. 75 patients were enrolled and divided into 4 groups depending on nosologies (genital herpes - 22 patients, herpes zoster - 18 patients, herpes simplex - 19; IM - 2 patients). It was shown that the drug is well tolerated, has minimal side effects. In GH therapy the drug is highly effective, 8.2-8.4-fold reducing the number of relapses, 2.5-fold increasing the interrecurrent period. In treatment of herpes zoster the maximum therapeutic efficacy was observed in the combination of Proteflazid® with acyclovir. In the treatment of herpes simplex drug's effectiveness was comparable with acyclovir. In the treatment of infection mononucleosis the effectiveness of the drug has been also noted, manifested in a positive clinical dynamics and stabilization of hematological parameters [6].

Isakov V.A., Yermolenko D.K. (2009, Russia) conducted an open, controlled clinical trial to determine the effectiveness of Proteflazid® in treatment of patients with recurrent GH. High clinical efficacy of the drug was demonstrated: 7.5-fold reduction in the relapse rate, 32% of patients had no recurrence within a year. Average parameters of interrecurrent period were increased2.8-fold. Positive dynamics was observed in the immunological parameters. After 6 months of treatment no herpes virus using direct immunofluorescence method was observed in 92% of patients [32].

In 2011 Romanyuk M. G. et al conducted a comprehensive study on the characteristics of treatment of patients with GH. Against the therapy background the positive dynamics, epithelialization was observed, on average, on day 6 of therapy. The average number of relapses in patients reduced from 6 to 3 within a year. The authors compared the efficacy of Proteflazid® and famciclovir but the incidence of adverse events in patients receiving Proteflazid® was significantly lower [33].

In the same year, researchers Bayev A.I. et al. (2011, Kazakhstan) published a series of reports on the study results of clinical and pathogenetic features and therapy differentiated approaches in mixed sexually transmitted infections (STIs). According to the results of observations, it was found that the use of Proteflazid® drug in treatment of mixed-STIs is an effective and safe method of treatment, which was confirmed by clinical improvement, normalization of immunological and biochemical parameters, lack of side effects and adverse reactions. [34]

In a subsequent study Ryzhko P.P., Roschenyuk L.V. (2012), Klimenko P.M. et al. (2012), Rak L.M., Yuzko O.M. (2013) also noted the positive dynamics of Proteflazid® administration as a regression of clinical manifestations, stable therapeutic response, and 1.5-fold reduced frequency of GH relapses with reduced duration of the course [35-37].

In 2015 Kornatskaya A.G. [38] and Benyuk V.A. [39] provided the results of two independent clinical studies for comparative evaluation of the efficacy and tolerability of Proteflazid® (suppositories) and Proteflazid® (drops in the form of vaginal tampons) in patients with herpetic and urogenital viral and bacterial infection.

The study presented by Kornatskaya A.G. (2015) involved 70 women with verified diagnosis of genital herpes (HSV-1, HSV-2) in the acute stage. Patients based on a simple randomization method were assigned to the main (n = 35) and control (n = 35) groups. Patients in the control group received the reference drug Proteflazid® (drops) in the form of vaginal tampons with a solution of the drug. By the end of therapy and during the 8-week period of observation a significant as compared with the baseline increase was observed in the level of local immunity (secretory Ig A, lysozyme, C_3 complement component). In particular, the level of secretory Ig A has risen to day 10 of treatment, remaining significantly high throughout the 8-week follow-up period (from 990.45 to 1825.24 μg/l); lysozyme level rose by day 10 of treatment, remaining significantly high throughout the 8-week follow-up period (from 28.39 to 41.31 μg/l); level of C_3 complement component – increased by day 10 of treatment and returned to baseline by the end of the 8-week follow-up period (from 17.68 μg/l of protein per screening to 81.17 μg/g of protein by day 10 and 20.37 μg/g of protein on week 8). After completion of the 10-day treatment period and 8-week follow-up the reduction as compared to baseline was observed in viral load of HSV DNA and a significant decrease in HSV markers level (Ig G, Ig M) [38].

All women involved in the study had the relief observed of clinical manifestations of genital herpes; the effectiveness of Proteflazid® (drops) drug treatment was 100%, with no recurrence observed of herpes infection. During the study it was shown that Proteflazid® (drops) is highly effective and well tolerated, no serious or unexpected adverse events were observed during treatment, laboratory parameters showed no negative changes [38].

Similar results were shown by Benyuk V.A. (2015) in a comparative clinical study in women with urogenital viral and bacterial infection [39].

However, the issue of chronic recurrent urogenital infections in adults should be considered not only from the standpoint of the complexity of therapy, but also in terms of the adverse effect on conception, pregnancy, and fetus.

Thus, according to the modern literature [40], one of the most frequent causes of maternal and perinatal morbidity and fetal mortality is intra-amniotic infection, in particular, various forms of HVI. The major complications in patients with HVI include threatened miscarriage, polyhydramnios and chronic fetal hypoxia, and during childbirth – premature rupture of membranes and anomalies of labor activity. The highest frequency of threatened miscarriages is attributable to recurrent form of herpes infection (73.3%). The development of infection is contributed by the suppression of cellular and humoral immunity during pregnancy due to physiological immunosuppression by reducing the number and activity of T and B lymphocytes, increased production of corticosteroids, estrogen, and progesterone. Primary HVI leads to spontaneous abortion in the early stages, appearance of congenital

malformations in fetus, and after 20 weeks – is one of the main causes of premature birth and placental insufficiency [40, 41].

Timely prevention of HVI relapses in patients at risk is a priority, but the use of toxic anti-viral drugs during pregnancy is limited. Proteflazid® according to preclinical studies has a high degree of safety, due to which was authorized for use in pregnant women and children.

Vdovichenko Yu.P. et al. (2003) were among first to conduct a comprehensive study of therapeutic and preventive efficacy of Proteflazid® in pregnant patients. The drug was administered to women with latent and recurrent forms of HVIs. Duration of therapy course was 21 days. In a latent form of herpes infection 1 course of Proteflazid® was prescribed, and in relapsed form – from 2 to 3 courses. Observations were performed in women in the course of pregnancy, starting from weeks 16-17 before delivery and at intervals of 2-3 weeks. It was found that therapy with Proteflazid® makes it possible to reduce the frequency of threatened miscarriage (from 73.3 to 36.7%), placental insufficiency (from 46.7 to 23.3%), pre-eclampsia of various severity (from 23.3 to 10.0%), preterm delivery (from 16.7 to 6.7%), premature rupture of membranes (from 46.7 to 20.0%) and abnormalities of labor (from 26.7 to 10.0%). In infants, a decrease was noted in the frequency of asphyxia of various severity (from 43.3 to 23.3%), manifestations of intra-amniotic infection (from 23.3 to 10.0%), lack of cases of generalized infection [42].

Simrok V.V., Gordiyenko E.V. (2003) examined the efficacy of Proteflazid® drug in treatment of viral infection in 34 (20 cases of GI and 14 cases of CMV) women of reproductive age with perinatal loss in history. It was established that Proteflazid® provides good clinical and immunological effects. Pregnancy occurs with significantly fewer complications, including the development of placental insufficiency, and ends as a rule, with timely delivery with the fetus in a satisfactory condition. [43]

Nagornaya N.F., Nikolayev S.V. (2006, 2007) conducted a series of studies on the prevention, treatment, and immunomodulating efficacy of Proteflazid® both in monotherapy and in combination with acyclovir in patients with HVI who experienced miscarriage. It has been found that the differentiated pregravid preparation and therapy during pregnancy with the inclusion of Proteflazid® reduces recurrence of herpes infection and risk of perinatal losses by 35%. The duration of relapse was 1.6-2-fold reduced; relapse rate was reduced to 1-2 cases within 8 months. In immunological terms there was an increase in the total number of T and B lymphocytes, normalized population structure of T-cells, decreased concentration of CIC [44-47].

Dolgov G.V., Abashyn V.G. (2009, Russia) confirmed the feasibility and effectiveness of Proteflazid® administration in couples of reproductive age with a history of pregnancy loss [48].

Benyuk V.O. et al. (2012) conducted an analysis of prevention and treatment of HVI in pregnant women with metabolic syndrome. 30 patients received the standard regimen of Proteflazid® during pregravid period (a period of 3-6 months) and during pregnancy. Against the background of the therapy a significant decrease was observed in clinical manifestations and shorter relapse of HVI (more than 1.4 times). The positive dynamics was observed of immunological parameters, obstetric and perinatal pathologies were reported rarely (by 50 %). The frequency of early miscarriages reduced from 73.3% to 36.7%, fetoplacental insufficiency from 46.7 to 23.3%. Use of the drug allowed 2-fold reduction in the incidence of disease in newborns [49].

These positive clinical and immunological results of Proteflazid® use in pregnant women against the background of active viral and bacterial mixed infection to reduce perinatal pathology were obtained by Azimova E.I. et al. (2011, Uzbekistan) and Reznichenko N. A. (2013) [50, 51].

In the absence of adequate treatment and monitoring for intrauterine infections the life prognosis for infants with HVI are extremely unfavorable. Mortality in congenital HVI in newborns can reach 30%, while the survivors have severe damage observed to the nervous system, multiple organ failure. If infection with HV in children occurred after birth, the clinical symptoms of the corresponding acute infection are non-specific and varied: children's erythema (HHV-6), aphthous stomatitis –"white mouth" (HSV-1, HSV-2), varicella (IVD), infection mononucleosis (IM) (EBV) mononucleosis syndrome (CMV). In children the infection process is often asymptomatic, but viruses ability of long-term persistence may potentiate the development of pathological processes in various organs and systems – broncho-pulmonary, cardiovascular, nervous, immune, and others over the years.. In this regard, the timeliness and adequacy of antiviral therapy depends on the physiological and mental harmony of the child's development. Proteflazid®, due to its high degree of safety, is the drug of choice in treatment of HVI in children from birth [2, 41, 52].

Kryuchko T.A., Nesina I.N. et al. (2002) were among the first to study the efficacy of Proteflazid® in treatment of neuroinfections in 20 children. The drug was administered to children in the age dosages for up to 4 months. The patients against the background of therapy were observed with distinct and lasting effect in dynamics of clinical and laboratory parameters: reduction of intoxication, improvement of general health, rapid relief of meningeal syndrome, correction of immunological disorders [52].

Yershova I.B., TA Goncharova T.A., , Skorodumova N.P. (2003) continued this direction of study. The authors noted that the use of a combination of exogenous interferon alfa-2b and Proteflazid® helps to prevent relapse and accelerates functional activity of children with viral meningoencephalitis [53].

According to Ovcharenko L.S. et al. (2004, 2006), in children with cytomegalovirus and chlamydia, as well as frequent ARVI the administration of Proteflazid® reduces the number of bacterial complications of acute respiratory viral infections, promotes correction of immunological parameters, which is associated with eradication of pathogenic organisms [54, 55].

Usachova O.V. et al. (2005) conducted a series of studies to assess the clinical efficacy and tolerability of Proteflazid® in treatment of fetal CMV infection in 23 infants and infectious mononucleosis (IM) in 38 children. The therapy administered in children with infection mononucleosis showed the recovery in 35.3% of patients. In 78.5% there was a gradual decrease in the manifestations of hepatomegaly, rapidly decreased ALT levels. In patients with CMV infection the leveling of cytolytic syndrome was observed, positive dynamics of neurological status, suppression of viral replication [41, 58].

In 2005 Chernysheva O.E. published data on study of the Proteflazid® efficacy in treatment of children with HVI. It was shown that against the background of treatment the acute manifestations of infection were relieved in 67% of patients, 64% –chronic recurrent course of HVI was translated into latent one, 2.5-fold reduction was observed in the number and duration of acute respiratory viral infection and complications [57]. The author having continued its study noted a relatively high efficacy of drug in relation to EBV [58].

Combination therapy scheme for CMV infection (a combination of Viferon and Proteflazid®) was studied by Turlibekova S.S. (2006, Kazakhstan).

She followed-up 48 children aged up to one year. Against the background of combination therapy in children on day 12 the positive dynamics was noted in clinical symptoms with complete elimination of the virus [59].

Nagornaya N.V., Vinogradov K.V. have studied in 2007 on the basis of the Pediatric Cardiac Surgery Department of V. C. Husak Institute of Emergency and Reconstructive Surgery of NAMS of Ukraine the efficacy of Proteflazid® in different courses of HVI in 27 children with congenital heart disease (CHD). The duration of the follow-up period was 12 months. According to study results 3, 12 months after completion of treatment no laboratory markers in children of active HVI were observed, and titers of specific IgG were reduced. The acute respiratory infections and bronchitis were recorded less frequently. [46]

The therapeutic efficacy of Proteflazid® in children with relapsing obstructive bronchitis on the background of recurrent HVI have been shown in studies of Shamsiyeva F.M., Mirsalikhova N.H. et al. (2011, Uzbekistan) [60].

Biletskaya G.A. et al. (2011) also studied the efficacy of Proteflazid® in IM treatment in 72 children. Their data supports the use of the drug in treatment of children with IM, reduces the duration of the disease manifestations and the duration of hospital stay, and reduces the possibility of relapse. [61]

In 2013 Znamenskaya T.K. et al. published data on the therapeutic efficacy of the unidirectional positive Proteflazid® drug in treatment of intrauterine infection in newborns from mothers with viral and bacterial infection. The drug was administered within a e month. The therapy significantly reduces the time of stay in intensive care department and use of mechanical ventilation, quick jaundice regress, less pronounced neurosonographic changes (ventricular dilatation), improved intracerebral hemodynamics [40].

According to the study results it can be concluded that in the pediatric practice for treating HVI Proteflazid® can be used with a high therapeutic effect.

It is known that HV has high affinity for the epithelium of the mucous membrane of the mouth and nasal cavity and therefore, they can cause both acute and chronic recurrent gingivostomatitis, cheilites, pharyngitis, treatment of which should be carried out taking into account the viral component of the disease.

Yakovets V.V., Belichenko Yu.N. (2004) studied the efficacy of Proteflazid® in treatment of herpetic lesions of the oral mucosa. Patients with oral mucosa gingivostomatitis were treated with Proteflazid®. Positive clinical dynamics was observed from the first days of therapy, epithelialization of aphthae - on day 3, recovery on day 6 of treatment. The appearance of the repeated eruptions in the acute period was recorded only in 8% of patients. Prolonged use of the drug showed a decrease in the frequency of recurrent relapses [62]. The effectiveness of Proteflazid® drug in treatment of herpetic gingivostomatitis in children was confirmed by data obtained in the studies by Gerasimov S.V.et al. (2006) [63].

In the extensive structure of neuroinfections HV lesions of the nervous system (NS) take a special place. The neuroinfections by a severity, diversity and peculiarities of clinical manifestations of HV can vary from mild subclinical to severe necrotic encephalitis, accompanied by a high mortality rate (80%). HV eye lesions (herpes keratitis, HK) may be an isolated manifestation of HVI, and may precede development of severe encephalitis. HK often recurs and causes the development of severe complications, such as corneal opacity,

secondary glaucoma, cataract, etc. The outcome of NS and eye lesions due to HV in these cases depends on timely and adequate antiviral therapy in the acute phase, and during convalescence [2].

The first studies, in terms of improving the antiviral regimens based on Proteflazid® in patients with HV-lesions of NS were conducted by Matyash V.I. et al. (2002). The author proposed two-stage therapy: stage 1 – selective antiviral therapy: acyclic nucleoside (up to 12 days) and Proteflazid® (up to 3 months); stage 2 – long-term restorative treatment using efferent therapy. It was found that the proposed scheme can reduce 2-fold the required dose of acyclovir (in relation to the recommended) and achieve sustainable impact on the restoration of function of affected organs and systems [64].

The effectiveness and usefulness of Proteflazid® in treatment of HK was rationalized for the first time in 2003 by Petrunya A.M., Vorotnikov S.V. The course of HK treatment with Proteflazid® was repeated if necessary 2-3 times a year. Against the therapy background the duration of corneal syndrome has decreased, compared with the control group, by an average of 3.5 ± 0.6 days, pericorneal injection – 3.1 ± 0.8 days, corneal edema – 2.8 ± 0.4 days. Increase in visual acuity after treatment in the study group was observed in 77.3% of patients. The development of inflammatory complications of HK in the group receiving the drug was observed. At the dispensary observation within 1 year HK recurrence in the study group was observed in 9.1% of patients [65].

In ophthalmic practice the data is also presented by Rykov S.O., Znamenskaya M.A. (2010) and Kamilov H.M. et al. (2011, Uzbekistan), which confirmed the previously marked Proteflazid® effectiveness in treatment of recurrent HK. The authors have found that the inclusion of the drug into HK treatment therapy promotes more rapid decrease in intensity of corneal syndrome, conjunctival secretions in the cavity, injection of the eyeball, corneal edema, and inflammatory infiltrate. Lysis of precipitates was observed for 1-1.5 months. The relapse rate was reduced to 5% compared to 16.6% of patients receiving conventional therapy [66, 67].

Specific effects of Proteflazid® on the immune and interferon status of patients with HV lesions of NS were presented in the publication by Goshko (Panasyuk) E.L. et al. (2005). It was shown that the patients receiving the drug had greater tendency to normalization of cellular immunity (increased total count of lymphocytes (CD3), natural killers (CD16), functional activity of neutrophils and mononuclear cells). Dynamics of interferonogenesis induction during treatment was characterized by a predominance of y-IFN activity within 2 to 9 days of drug administration, with a consequent increase in α-IFN on day 10. Time of interferon conversion coincided with the time of clinical onset of the positive dynamics. Against the background of long-term (up to 3 months) daily use of the drug the suppression of α-- and y-IFN activity was not observed, indicating the absence of refractoriness of immunotropic cells to IFN induction [68].

A year later, the data were published by Panasyuk E.L. (2006), demonstrating the efficacy of Proteflazid® etiopathogenic therapy in patients with HV lesions of NS. It was shown that Proteflazid® monotherapy for moderate uncomplicated HVI has a moderate clinical and immunological effectiveness manifested in regression of somatic-neurological symptoms on day 8 ± 2.6 of treatment; seroconversion of specific antiviral antibodies on month 2.0 ± 0.8 of treatment; increasing in the number of NK-cells by 17%, functional activity of mononuclear cells by 20%, neutrophils by 10 % and 1.5-fold reduction in intensity

of neurological and autoimmune reactions. Use of the drug during the period of recovery can reduce the frequency of repeated clinical and virological relapse ("+" virus) by 1.9 times, clinical virus ("-") relapses – 1.3 times, reduce the severity of the disease and accelerate the achievement of therapeutic effects during repeated therapy recurrence [69].

Chopyak V.V., Potemkina G.O. (2008) studied the effect of Proteflazid® on clinical, immunological, and virological indicators of patients with chronic EBV infection in adults in the process of reactivation. The study demonstrated that 80% of patients receiving the drug had a significant improvement in overall health status. The immunological parameters showed an increase in mass killing subpopulation of lymphocytes due to cytotoxic T lymphocytes, functional capacity of NK cells to the synthesis of interferon, suppressive activity was reduced of regulatory CD4 +/CD25+ lymphocytes, increased phagocytic activity of neutrophils, acquired and congenital antiviral immunity was activated [70].

Thus, the presented results of studies indicate the pathogenetic validity and effectiveness of Proteflazid® (drops) in treatment of HV lesions of NS and eyes.

As is known, HVIs play an important role in the development of various somatic pathology as a result of the direct impact of viruses on the organs and tissues, and indirectly, through the development of immunological disorders. In this regard, the prescription of Proteflazid® with immunomodulating and antiviral purpose may potentiate the effect of combination therapy in these patients.

Sidorenko E.V., Driyanskaya V.E. (2007, 2010) conducted studies on the clinical and microbiological (60 patients) and immunologic (25 patients) Proteflazid® effects in patients with chronic uncomplicated pyelonephritis, in the blood of which the diagnostic elevation was observed in antibody titers (IgG) to *Herpes simplex virus, Cytomegalovirus, Toxoplasma gondii and / or Chlamydia trachomatis.* A significant reduction was observed in proinflammatory cytokines in blood and urine, indicating a more active relieving of inflammation. The parameters returned to normal of antioxidant protection lipids peroxidation system (LPO-AOD), clinically observed decrease in the frequency of relapses and prevented kidney failure [71, 72].

The effectiveness of Proteflazid® and Viferon in children with hematuric form of chronic pyelonephritis and related chronic EBV infection was studied by Borisova T.P., Tolchennikova E.N. (2013). It was noted that during the treatment most patients had signs leveled of virus activity, decreased frequency of registration of haematuria, improved renal function, there was a correction of interferon status, 2.7-fold increase in α-IFN levels, 3.6-fold – y-INF while reducing the level of IFN anti-inflammatory cytokines [73].

Kolesnik M.O. et al. (2014) continued the study in this area. They followed-up adult patients with pieloneflitom. Some of the patients in addition to antibiotic therapy received Proteflazid®. It has been established that Proteflazid® contributes to normalization of cytokine background in blood and urine; ensures eradication of pathogens (especially herpes simplex virus and ureaplasma) [74].

As seen from the above observation results, Proteflazid® (drops) is widely used by practitioners in Ukraine, Russia, Kazakhstan, and Uzbekistan and included in various schemes of treatment and prevention of herpes and viral and bacterial infections in children and adults. Upon marketing authorization to use Proteflazid® in clinical practice more than 65 clinical studies and observations were conducted within the last 15 years to study the efficacy and safety of the drug against herpes and viral-bacterial infections, involving more than 3,200

patients receiving Proteflazid® (drops), including children and pregnant women. The main results of the observations are presented in the table.

Table

Main results of clinical studies of Proteflazid® (drops) efficacy and safety in children and adults within a period of 2000-2015

№	Authors, year and source	Number of patients		Main results of Proteflazid® use in clinical practice
		Total	Receiving drug	
1	Ventskovsky B.M. 2000, [15]	60 adults	40	Proteflazid® in treatment of primary and recurrent infections caused by Herpes genitalis is characterized by high efficiency, with no serious side effects. The complete elimination of the clinical manifestations of the disease by day 5-7 of treatment was observed in 60% of patients, recovery for all patients occurred up to day 10 of drug administration.
2	Vovk I.B. et al 2002, [16]	68 adults	68	There was a normalization of the main factors of cervical mucus protective function (slgA, immunoglobulins, lysozyme and C_3 component of complement), decreased reproductive tract microflora contamination that has a positive effect on the state of local immunity of the female genital tract as a whole. In 85.3% of women, according to PCR data, the virus was not detected, no Ig observed in 91.2% .
3	Kryuchko T.A.et al, 2002, [52]	20 children	20	There was a reduction of intoxication, improvement of health, rapid relief of meningeal syndrome, recovery in CD4±/CD8+ ratio (1.3 ± 0.32), increased immunoglobulins in blood serum Tg G (8.4 ± 1.8); Tg A (3.3 ± 0.05); Tg M (0.4 ± 0.03).
4	Matyash V.I. et al, 2002 [64]	25 adults	25	Proteflazid® with efferent methods of treatment reduces 2-fold the required dose of acyclovir (in relation to the recommended) and achieves sustainable effect on function recovery of affected organs and systems.
5	Yu. P. Vdovichenko et al, 2003 [42]	120 pregnant	30	Proteflazid® can significantly reduce the incidence of threatened miscarriage (from 73.3 to 36.7%), placental insufficiency (from 46.7 to 23.3%), preeclampsia of varying severity (from 23.3 to 10.0%) , preterm delivery (from 16.7 to 6.7%), premature rupture of membranes (from 46.7 to 20.0%) and abnormalities of labor (from 26.7 to 10.0%).
6	Grinkevich T.M., 2003 [21]	20 women	20	Proteflazid® facilitates the course of the disease, reduces the frequency of relapses, prolongs interrecurrent period. It increases phagocytic activity of neutrophils, stabilizes cellular immunity.
7	Yershova I.B et al, 2003 [53]	86 children	86	Reducing in frequency of relapses, complications, reducing the period of recovery of children after meningoencephalitis.

8	Lutsyk B.D. et al, 2003 [75]	25 adults	25	After the treatment the clinical healing was observed of cervical erosion in 15 patients out of 25. All 35 patients after treatment had only individual cells infected by viruses. In 7 patients symptoms disappeared of chronic fatigue, discomfort in the abdomen, which often occurs prior menstruation
9	Petrunya A.M.., Vorotnikov S.V., 2003 [65]	47 adults	22	In the course of treatment in the study group the positive dynamics was observed of clinical parameters. In the main group the duration of the corneal syndrome was reduced by an average of 3.5 ± 0.6 days compared to the comparison group (P <0.05), pericorneal injections - 3.1 + 0.8 days (P <0.05), corneal edema - 2.8 + 0.4 days (P <0.05).
10	V. V. Simrok, Gordiyenko E.V., 2003 [43]	34 adults	19	Proteflazid® in women for complex treatment of CMV and HI contributed before pregnancy to the stabilization of the level of antibodies to specific IgG level within the normal range in the majority of patients (in 8 of 11 pregnant patients) due to the lack of Ig M in all 11 pregnant women. All surveyed pregnant women of the main group had delivery on time with an infant average weight of 3340 ± 55 g with this value in comparison group of 2096 ± 30 g
11	Fedotov V.P. et al, 2003 [76]	34 adults	34	Already on day 2-3 of treatment new rashes ceased, tendency was observed to epithelialization of erosions and a decrease in the severity of subjective sensations. Complete resolution of clinical manifestations of the disease when using Proteflazid was noted on day 5-7 of administration of the drug in 23 (69.1%) of the observed patients, day 8-9 - in 11 (30.9%). Clinical recovery was observed in 25 (70.9%) patients in complex treatment that included Proteflazid, a significant improvement in 9 (29.1%). No lack of effect or worsening of the disease when using Proteflazid was observed. In the group of patients treated with the addition of complex therapy Proteflazid®, positive clinical picture was observed in 81.8% (in the control group - 72.7%), stable microbial effect cure chlamydia occurred in 90.9% (against 63.6% in control group), recurrence of herpes lesions was observed in 18.2% of the observed. No side effects of the drug both topically and inside, were observed
12	Shvedyuk S.V., 2003 [77]	22 adults	11	In the group of patients treated in addition to complex therapy with Proteflazid®, positive clinical patter was observed in 81.8% (in the control group - 72.7%), stable microbial effect of cured chlamydia occurred in 90.9% (vs 63.6% in control), recurrence of herpes lesions was observed in 18.2% of patients. No side effects of the drug used both topically and orally were observed
13	Andriyets O.A. et al, 2004 [17]	20 children	10	After 1 week of dosing 40% of patients had significantly reduced clinical manifestations and complaints, after 2 weeks of treatment in 85% of patients rashes disappeared completely in the genitals, as well as subjective sensations.
14	Ovcharenko L.S. et al, 2004 [54]	60 children	60	Proteflazid® exhibits activity against intracellular pathogens (CMV, chlamydia), that allows recommending it for use in a program of treatment of children for both acute and chronic forms of the disease. Repeated treatment of resistant forms allows in 1,5-2 months normalizing the laboratory parameters in 100% of cases.

15	Kishakvich I.T., 2004 [19]	170 adults	31	Normalized levels of immunoglobullins, lysozyme in the cervical mucus, SIgA levels increased significantly with a parallel decrease in the level of IgM, indicating the activation of humoral immunity and reduced antigenic load due to the reduction of genital infection.
16	Nikiforova T.O. et al, 2004 [78]	26 adults	14	Proteflazid® has a pronounced efficacy in treatment of patients with EBV-infection. It provides for quick disappearance of intoxication, lymphoproliferative effects, restored liver function, significantly reduced IgG blood level.
				Increased body temperature and general condition returned to normal in 76.8% of patients receiving the drug, vs 50.0% of those in the control group. Reduced lymphadenopathy was observed in 35.7% of patients vs 25.0% - in the control group.
17	Andriyets O.A., 2005 [18]	279 children	42	Increased levels of IL-1β, IL-2, and TNF-α in peripheral blood and IL-1β, sIgA in vaginal secretions during treatment and after the course of treatment, indicating the process of recovery and repair.
18	Gley A.I., 2005 [79]	47 adults	27	A clear positive dynamics was described in the form of a rapid decrease in the size of lymph nodes and spleen, improved hemogram parameters (reduced number of leukocytes, disappearance or reduction in atypical mononuclear cells count) and biochemical parameters (normalization or reduction in transaminase activity). After 2 months the viremia was observed in 48% of patients taking the drug and 98% in the control group.
19	Romashchenko O.V., Redunko A.V., 2005 [80]	60 women	30	Proteflazid® in treatment of inflammatory diseases of the genitals caused by mixed infection has clinical, microbiological, immunological efficacy compared to traditional methods of treatment of this disease. The incidence of relapse during basic therapy was 16.6%, and while taking Proteflazid® - 5.0% ($p < 0.05$).
20	Usachova O.V. et al, 2005 [81]	38 children	17	Proteflazid® administration resulted in recovery of 35.3% (in control group – 19.1 %) of patients. In 78.5% of children taking the drug, there was a gradual decrease in the manifestations of hepatomegaly, and 75% of children with cytolytic syndrome had rapidly decreased ALT levels.
21	Usachova O.V., 2005 [41]	23 children	23	Against the background of treatment with Proteflazid® in all cases, regardless of the clinical form of the disease, there was achieved a positive serological result. This was manifested in the disappearance of immunoglobulin M against CMV and reduced count of anti-CMV IgG. Positive dynamics was achieved in children with intrauterine CMV infection as to the clinical symptoms and stabilization of specific immunological parameters.
22	Chernysheva O.E., 2005 [57]	199 children	199	The therapy resulted in a relief of acute manifestations of the infection in 67% of patients, changed to the chronic recurrent course of herpes virus infection into latent one – 64%. All children observed had 2.5-fold reduction in the amount and duration of recurrent respiratory diseases and complications.
23	Goshko E.L. et al, 2005 [68]	68 adults	35	Patients of the main group while taking Proteflazid had a more pronounced tendency to normalization of cellular immunity (increasing in total number of lymphocytes (CD3), natural killer cells (CD16), functional activity of neutrophils and mononuclear cells). Dynamics of

				interferonogenesis inducing activity was characterized by a predominance of y- IFN on day 2 through 9 of treatment, with a consequent increase in α-IFN on day 10. Interferon conversion time coincided with the timing of clinical onset of positive dynamics.
24	Grinkevich T.M., 2005 [21]	120 adults	49	The treatment resulted in elimination of imbalance between cellular and humoral immunity, positive clinical effect was observed in 82,7% of cases, reduced frequency of relapses by 19%; normalized vaginal microbiocenosis in 83.6% of women, accelerated re-epithelialization at herpetic endocervicitis, reduced psycho-emotional stress, without causing side effects.
25	Bilyk N.M., 2005 [80]	40 pregnant	20	In patients treated with combination therapy, the number of fixed-term birth was twice as much as the number of missed abortion and miscarriage - half as compared with the group of patients treated only with maintenance therapy.
26	Lesovoy V.N., Yakovleva E.V., 2006 [27]	54 adults	30	Prescription of Proteflazid® to patients with genital herpes can significantly increase the effectiveness of treatment by 15-20%. Furthermore, the positive effect is more sustained. Significantly improved is the general condition of the patients body, normalized immunological parameters, the clinical manifestations of herpetic prostatitis compensated.
27	Gerasimov S.V. et al, 2006 [63]	38 children	17	There was a more rapid dynamics of aphthous elements dissappearance (an average of 5 days of therapy), temperature normalization, disappearance of salivation and pain. Use of Proteflazid® reduced relapses of the disease: in the control group the frequency of re-treatment over gingivostomatitis was 3/10, while in the group treated with Proteflazid® no child had a relapse -0/10 (p = 0.077).
28	Gopchuk O.M., 2006 [23]	70 adults	35	Women who received proposed therapy had a significant increase in the number of CD4 + lymphocytes and NK-cells to normal values, increase in the number of IFN-y and IFN-α, more pronounced positive indicators in immunogram, normalization of the menstrual cycle, absence of recurrence of genital herpes and normalization of vaginal microbiocoenosis.
29	Zapolsky M.E., 2006 [25]	30 adults	30	A positive response in all patients already on day 4-5 of treatment, complete resolution on day 5-6 in 70% of patients. Confirmed high efficacy in the treatment of genital herpes.
30	Panasyuk E.L., 2006 [69]	236 adults	159	Marked regression of somatic-neurological symptoms on day 8 ± 2.6 of treatment; seroconversion of specific antiviral antibodies on month 2.0 ± 0.8 of treatment; increased number of NK-cells by 17%, functional activity of mononuclear cells 20%, neutrophils 10% and 1.5-fold reduction of severity of neurological and autoimmune reactions. The drug reduced the frequency of repeated clinical and virological relapse ("+" virus) – 1.9-fold, clinical virus ("-") – 1.3-fold.
31	Nagornaya V. F., Nikolayeva S.V., 2006, [44]	60 adults	30	Proteflazid® in patients with habitual miscarriage on the background of HI helps to reduce relapses and risk of perinatal losses. The duration of relapse was reduced in the majority of patients – 1,6--fold, relapse rate - up to 1-2 cases within 8 months.

32	Ayzyatulov R.F., 2006 [29]	30 adults	30	Complex therapy of mixed urogenital infection with Proteflazid is effective, does not cause side effects, well tolerated by patients. Positive clinical dynamics was observed already on day 3-5 of treatment; day 6-8 – ceased discharges, most patients had elimination of the pathogen.
33	Nagornaya V.F., Nikolayeva S.V., 2007 [45]	80 pregnant	40	Proteflazid® in pregravid preparation and correction during pregnancy in patients with chronic HVI and NB history contributes to the correction of the immune system function and reduces the antigenic load.
34	Nagornaya V.F., Vinogradov K.V., 2007 [46]	27 children	27	After treatment with Proteflazid® 3 and 12 months after 26.0 ± 9.1% of children who had acute and/or exacerbation of chronic HI had no laboratory activity markers of the process, 73.9 ± 7.0% of patients with latent form had a significant decrease in titers of specific IgG. Study of catamnesis showed a significant ($p < 0.05$) decrease in the frequency of acute respiratory viral infections during 1 year in 47.8 ± 10.4% of studied patients, acute bronchitis – 34.7 ± 9.9%, and a significant decrease of frequency and severity of the complications of respiratory tract infections – 39.1 ± 10.1% of patients.
35	Nikolayeva S.V., 2007 [47]	140 pregnant	100	There was a correction of immunological disorders, improvement of fetoplacental complex function. Reduced recurrence of herpes infection by 70%, threat of miscarriage by 55%, placental dysfunction by 35%, premature births by 29.5% and total perinatal losses by 35%.
36	Sidorenko E.V., Driyanskaya V.E., 2007 [71]	40 adults	25	There was a significant reduction of pro-inflammatory cytokines, indicating a more active relieving of inflammation. Returned to normal blood LPO-AOD that was considered as a potentiated effect of the drug on antibiotic therapy.
37	Shymanskaya I.G., 2007 [28]	32 adults	32	As a result of treatment in 15 patients (46.9%) the episodes of herpes recurrences were absent during therapy, 9 (28.1%) noted a reduction in the duration of the activity and clinical symptoms, 28 (87.5%) after treatment had no genital herpes detected by PCR, and virus has not been identified in 7 patients with asymptomatic course of genital herpes.
38	Gerasimova T.V., Gopchuk O.M., 2007 [24]	150 adults	150	Clinical effectiveness of the proposed scheme of treatment was 82.8%. During the treatment no exacerbations of inflammation were observed, biocenosis returned to normal, in 64% of women PCR for HSV was negative; recurrence of herpes infection was reduced 2--fold.
39	Gley A.M., 2008 [81]	258 adults	112	Proteflazid®, as a monotherapy according to the developed scheme significantly reduces the duration of viremia during 2 months, compared with patients who did not receive antiviral therapy
40	Sundukov A.V. et al, 2008 [6]	75 adults	75	Proteflazid® reduces 8.2-8.4 fold the number of relapses, 2.5-fold increases the interrecurrent period. In treatment of herpes zoster maximum therapeutic efficacy was observed in combination with acyclovir. In treatment of herpes simplex Proteflazid® effectiveness is comparable to acyclovir. In treatment of infectious mononucleosis the effectiveness of the drug has been noted, which manifested in a positive clinical dynamics and stabilization of hematological parameters.
41	Flax G.A., 2008 [30]	55 adults	35	The decrease was achieved in the frequency of exacerbations, normalization of laboratory parameters (disappearance of virus in PCR assays, reduction and/or disappearance of the antibody titer by ELISA

				in acute manifestations of GH which is especially important in the period of remission.
42	Chopyak V.V., Potyomkina G.O., 2008 [70]	25 adults	25	Proteflazid® contributes to a significant improvement in the general state of health in the majority (80%) of patients, regression of the main symptoms. It has immune adjusting effect, helps to increase the mass of killing subpopulation of lymphocytes by cytotoxic T lymphocytes, functional ability of NK-cells to the synthesis of interferon, reduces suppressive activity of regulatory CD4+/CD25+ lymphocytes, increases the phagocytic activity of neutrophils, thus activating the acquired and innate antiviral control.
43	Popova T.V., 2008 [31]	128 adults	98	It has been found that the overall efficiency of the repeated course of therapy was 93.8%, the majority of patients experienced stable regress of inflammation symptoms, normalization of the vaginal microflora.
44	Долгов Г.В.Dolgov G.V., Abashyn V.G., 2009 [48]	62 adults	34	After treatment of patients of the main group the most favorable adaptation reaction, compared with baseline, increased significantly by 60%. The increase in the natural resistance of the main group is demonstrated by the change analysis in system parameters of neutrophil granulocytes after complex treatment with Proteflazid®. It has been shown that administration of the drug significantly increases the bactericidal action of blood serum and phagocytosis.
45	Isakov V.A., Yermolenko D.K., 2009 [32]	25 adults	25	The relapse rate was 7.5-fold reduced and clinically milder relapses were observed, 32% had no recurrence during the year. Averages interrecurrent period increased 2.-fold. Positive dynamics was observed in the immunological parameters. After a course of treatment in 23 patients (92%) no herpes virus for 6 months was detected by direct immunofluorescence method.
46	Rykov S.O., Znamenskaya M.A., 2010 [66]	134 adults	50	Proteflazid® contributed to a more rapid improvement in clinical ophthalmological examination in most patients. The dynamics of treatment showed a rapid decrease in the intensity of corneal syndrome, conjunctival discharge in the cavity, corneal edema, and inflammatory infiltration. Use of the drug reduced the duration of the treatment of patients (on average 4-5 days) and reduced relapse incidence by 36%.
47	Sidorenko E.V., 2010 [73]	60 adults	25	Proteflazid® in combination therapy resulted in a more pronounced clinical and microbiological effects, as well as lower production of proinflammatory IL-8, prosclerotic TGF and antibodies to ET.
48	Kamilov H.M. et al, 2011 [67]	38 adults	38	A rapid resolution of symptoms, recovery of visual acuity (88.9% of cases). Lysis precipitates for 1-1.5 months. The relapse rate was reduced to 5%.
49	E. I. Azimova, et al, 2011 [50]	60 pregnant	30	Combined therapy with the inclusion of Proteflazid® drug prevents the development of immunodeficiency, improves the function of the placenta, which reduces the obstetric and perinatal complications in women with recurrent herpes infection.
50	Romanyuk M.G. et al, 2011 [35]	580 adults	312	The therapy showed a positive clinical dynamics, epithelialization was observed by an average on day 6 of therapy (in comparison group - on day 8). The mean number of relapses in patients was reduced from 6 times a year to 3.

51	Turlibekova S.S., 2011 [59]	48 children	23	Children on day 12 had the positive dynamics observed of clinical symptoms with complete elimination of the virus. After 1 year of treatment SLPI levels in blood of study group patients significantly decreased and did not differ from the normal range (1260 ± 101 vs. 1122 ± 76 pg/ml, in contrast to the control group of patients with higher values (1433 ± 66 pg/ml).
52	Shamsiyev F.M. et al, 2011 [60]	169 children	169	Using of a new therapy regimen with Proteflazid® prolonged the remission and thus, demonstrated not only more pronounced therapeutic effect, but also an anti-resistant one. It was shown that a double effect (immune adjusting and antiviral) of the drug is enhanced by the application of the new scheme.
53	Bayev A.I. et al, 2011 [34]	345 adults	80	It was established that Proteflazid® in treatment of mixed-STI is effective and safe, which was confirmed by clinical improvement, normalization of immunological and biochemical indicators, absence of side effects and adverse events.
54	Biletskaya G.A. et al, 2011 [61]	75 children	30	It was established that Proteflazid® in treatment of children with IM reduces the duration of symptoms of the disease manifestation and duration of hospital stay, reduces the possibility of recurrence.
55	Zapolsky M.E., 2012 [26]	88 adults	32	Against the background of therapy the epithelialization of erosions and bullous elements in 96.9% of patients in main group resolved on day 9-10 of treatment. Repeated relapse within a year of magnetoelectric effect was observed in 12.5% of patients. Proteflazid® in treatment of HMEE has immunocorrecting, antioxidant, detoxifying effect, which is extremely important for the herpes-induced autoimmune processes.
56	V. O. Benyuk, et al, 2012 [49]	90 pregnant	30	Positive dynamics in immunological terms, rarely reported – by 50% – obstetric and perinatal pathology, abortion rate in the early period decreased from 73.3% to 36.7%, fetoplacental insufficiency from 46.7 to 23.3%; premature births from 16.7% to 12.0%; premature rupture of the membranes from 46.7 to 20%; development of anomalies of labor activity from 26.7 to 10%. Use of the drug allowed decreasing by half the incidence of disease in the newborn: asphyxiation from 43.3% to 23.3%; manifestations of intra-amniotic infection from 23.3% to 10%, the development of generalized infection from 11.3% to 0%.
57	Ryzhko P.P., Roshchenyuk L.V., 2012 [35]	110 adults	110	Proteflazid®, as monotherapy, reduces the duration of disease recurrence with an average of 7.7 ± 0.1 to 4.8 ± 0.08 days, 85 (77.3%) patients had a decrease in the severity of the disease, as well as frequency of relapse by more than 2-fold.
58	Klimenko P.M., et al, 2012 [36]	40 adults	30	The therapy resulted in positive clinical dynamics (regression of lesions, reduced itching, burning), an average on day 4 a 1.5-fold reduction was observed in the duration of relapse and reduced frequency of relapses.
59	Rak L.M., Yuzko O.M., 2013 [37]	64 adults	32	The therapy resulted in positive dynamics of regression of clinical manifestations, stable therapeutic response (after a month of observations) and a decrease in the frequency of relapses.
60	Reznichenko N.A., 2013 [82]	200 pregnant	200	The therapy in most patients resulted in regression of clinical manifestations of vulvovaginitis, vaginal microflora was returned to normal, reduced (1.77-fold) the frequency of registration of diagnostically significant pathogens. The immunological parameters

				showed a positive correction in the system and local immunity, decreased levels of pro-inflammatory cytokines. 73% of women gave birth to healthy children.
61	Borisova T.P., Tolchennikova E.N., 2013. [73]	54 children	54	The therapy in most patients leveled signs of virus activity, decreased frequency of registration of haematuria, improved renal function, there was a correction of interferon status, 2.7-fold increase in α-, 3.6-fold in y-IFN levels and reduced proinflammatory cytokines.
62	Znamenskaya T.K. et al, 2013 [40]	110 children	40	The therapy reduced the stay of patients in intensive care department and use of mechanical ventilation, resulted in jaundice quick regression, less pronounced neurosonographic changes (ventricular dilatation), improved intracerebral hemodynamics.
63	Kolesnik M.O. et al, 2014 [74]	83 adults	20	Proteflazid® helps to normalize cytokine in blood and urine, indicating the relief of inflammatory reactions. A more rapid eradication of pathogens (herpes simplex virus and ureaplasma), which was manifested in a decrease in titers of specific IgG antibodies.
64	Kornatskaya A.G., 2015 [38]	70 adults	70	An increased level of local immunity was observed. In particular, the level of secretory Ig A has risen on day 10 of treatment, remaining significantly high throughout the 8-week follow-up period (from 984.32 to 2496.19 μg/l); lysozyme level rose by day 10 of treatment, remaining significantly high throughout the 8-week follow-up period (30.06 to 51.67 μg/l); C_3 complement component level increased by day 10of treatment and returned to baseline by the end of the 8-week follow-up period (from 17.99 μg/g of protein at screening to 37.47 μg/g of protein on day 10 and 20.37 μg/g of protein on week 8). In both test groups there was significant, compared with baseline, reduction in viral load of HSV DNA. After 10-day course of treatment, and after completion of 2- and 8-week follow-up period no HSV DNA in swab-scrapings from the epithelium of the mucous membrane of the vagina/cervix was observed. All subjects experienced significant compared to baseline reduction of HSV markers (Ig G, Ig M) after 10 days of treatment, 2 and 8 weeks of the follow-up period.
65	Benyuk V.A., 2015 [39]	70 adults	70	The evidence of the effectiveness of the therapy was a significant increase in local immunity. In particular, the level of secretory Ig A and lysozyme levels has risen by day 14 of treatment, remaining significantly high throughout the follow-up period; level of C_3 complement component increased by day 14 of treatment and returned to baseline by the end of the 4-week follow-up period (24.7 μg/g protein - at screening; 33.0 μg/g protein – on day 14; 24.5 μg/g of protein – by the end of 4-week follow-up). It was noted significant compared with baseline decrease in viral load of HSV DNA. After completion of the 14-day treatment period and 4-week follow-up period no HSV DNA in swab-scrapings of vaginal mucous epithelium/cervix was observed. All subjects experienced significant, compared with the baseline, reduction in the frequency of detectable chlamydial DNA.

Conclusions

The systematic review of scientific literature devoted to the results of pre-clinical study indicates the presence in the active ingredient of the Proteflazid® of direct antiviral action against herpes viruses containing DNA. Proteflazid® has poly-pharmacological effect: it blocks the synthesis of virus-specific enzyme – DNA polymerase and thymidine kinase in herpes infected cells, induces the synthesis of endogenous y- and α-interferon, has antioxidant activity, has apoptosis modulating action, strengthening the direct antiviral effect through mediated antiviral activity.

A systematic review of the literature devoted to the results of the clinical use for many years of Proteflazid® (drops) demonstrates the presence of a wide spectrum of antiviral action against herpes viruses, which, in turn, confirms the validity of the results of pre-clinical phase of study and the effectiveness of the drug in treatment of diseases caused by viruses herpes under clinical conditions.

A detailed analysis of the results of post-registration clinical studies indicates a broad application of Proteflazid® (drops) in children and adults (including pregnant women) in clinical practice of infectious diseases, pediatrics, ophthalmology, dentistry, gynecology, neonatology, urology, neurology for treatment of diseases caused by HVs. Long-term results of observations show a decrease in the frequency of HVI relapses after use of Proteflazid® (drops). On the basis of scientific evidence of these materials, it can be argued that Proteflazid® (drops) is the ethiopathogenetically rationalized drug of choice in treatment of various clinical forms of HVIs both in children and adults at the acute phase and during convalescence.

High clinical efficacy and safety are confirmed by the results of Proteflazid® (drop) use in treatment of more than 3200 patients (adults, children, pregnant women) during more than 65 clinical trials with the coincidence of the results focus of treatment. The drug was well tolerated, with no side effects. Preclinical and clinical studies suggest that Proteflazid® (drops) contributes to the persistent therapeutic effect on eradication of herpes viruses and reduces the frequency of HVIs relapses.

Given the high efficacy and safety of Proteflazid® (drop) in HVIs treatment its use is justified and implemented in the methodical recommendations and circulars in Ukraine and abroad.

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