Modern drugs and technologies

APPLICATION OF ENTEROSGEL ENTEROSORBENT FOR TREATMENT OF INTOXICATION AND DIARRHEA SYNDROMES IN PATIENTS WITH AIDS DURING ANTIRETROVIRAL THERAPY

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Intoxication is a clinical manifestation of pathological conditions arising from influence of toxic substances of endogenous and exogenous origin on the body. Intoxication syndrome may accompany many pathological conditions, including infectious diseases, HIV infection as well as viral hepatitis. Liver disease in HIV infection may be associated with the action of both HIV virus and HBV, HCV, EBV, CMV, infection caused by MAC complex as well as toxic action of Highly active antiretroviral therapy (HAART) [1, 2].

Many drugs used for the treatment of HIV infection can cause nausea and vomiting in the patients. Especially often these symptoms are expressed after administration of abacavir, lamivudine, zydo-vudyne and stavudine [2]. Diarrhea is often caused by administration of nelfinavir and lopinavir as well as ritonavir [9]. Some preparations used for treatment of concomitant diseases in HIV-positive parients in (rifampicin, izoniazid, fluconazole, itraconazole, ketoconazole, biseptol, lamivudine, stavudine, nevirapine, ritonavir), can cause increased activity of serum aminotransferase [2, 3, 4].

Mitochondrial toxicity (including lactate acidosis, hepatotoxicity, pancreatitis, peripheral neuropathy) associated with taking nucleoside inhibitors of reverse transcriptase and is often caused by adminstration of stavudine, more seldom - by adminstration zidovudyne, lamivudine and abacavir [3].

Gastrointestinal tract (GIT) is most badly affected by antiretroviral drugs, as it is the "first-line" immune protection of the body which aims to prevent absorption of potentially hazardous substances and microorganisms in the blood flow. Although HAART drugs are necessary to reduce HIV viral burden for GIT, they are considered to be "potentially poisonous" and lead to activation of protective mechanisms to output "the poison" from the body until it is not included in the blood flow [6-8]. If nausea, vomiting and diarrhea are significant and have long duration, it can lead to significant violations of water-electrolytic balance and reduce HAART drugs level in the blood. It is also very important to eliminate the therapy side effects [8].

One of known methods of eliminating intoxication is enterosorption, easy to use and relatively safely, which is possible to conduct both on an outpatient basis and at home. Enterosorbents are drugs of different structure that are able to bind endogenous and exogenous toxic substances in the GIT by way of adsorption, absorption, ion exchange and complex formation. Inclusion of enterosorption in the comprehensive treatment of viral hepatitis and HIV leads to a rapid decrease of such toxic substances as molecules with low and medium molecular weight in the blood (MSM) [10].

Entherosgel enterosotbent (hydrogel of methylsilicic acid) has a detoxication effect associated with

absorption (through the mucous membrane of capillaries in the intestine) of endo- and exotoxins, pathogens of various diseases (bacteria and their toxins, viruses), toxic metabolites (creatinine, bilirubin, bile acids, some regulatory peptides), radionuclides and other xenobiotics in the intestine and blood. In infectious diseases the drug, along with its detoxification effect has also expressed antidiarrhea effect [11, 12]. In the recent years it was found that Entherosgel absorbs almost no oral drugs, which makes its application possible in the treatment of many diseases without the risk of reduction of therapeutic concentrations of major drugs and, consequently, the effectiveness of treatment [13].

Objectives: to determine the effectiveness of Enterosgel enterosorbent in the treatment and prevention of (relapse) intoxication and diarrhea syndromes in AIDS patients with HAART therapy.

PRODUCT								
ENTEROSGEL						ENTEROSGEL		
0 days		15 days		1 month		1,5 months		2 months

Table 1. Results of the first and the second examination of the patients (before and after the first administration of Enterosgel for the patients in both groups)

Group	Examination №	LII	NII	HII	Leukocytes, 10^6/l	% eosinophiles	% band neutrophiles	Erythrocytes, 10^{12}/l	Hb, g/l	ALT, U/l	AST, U/l	General bilirubin, μmol/l	Direct bilirubin, μmol/l
Main	1	2,67±1,47	0,21±0,1	3,84±4,37	5113±3392	0,025±0,026	0,051±0,028	3,54±0,99	109,14±27,08	51,6±30,2	59,2±42,5	9,5±3,12	2,34±1,94
	2	2,16±1,02	0,2±0,14	2,91±1,66	4945±1763	0,022±0,024	0,033±0,022	3,68±0,82	112,45±21,37	52,6±43,3	55,1±45,6	12,4±11,7	3,7±5,9
Control	1	2,29±0,95	0,23±0,10	2,51±1,78	4876±1887	0,032±0,023	0,046±0,035	4,28±0,57	130,04±15,61	50±51,7	53,9±93,5	13,3±4,34	2,76±2,58
	2	2,39±0,91	0,22±0,12	2,86±1,35	5106±1670	0,039±0,027	0,048±0,028	4,14±0,44	128,54±17,42	51±48	50,8±36,2	11,5±3,4	2,9±1,7

Table 2. Results of the third and the fourth examination of the patients (before and after the second administration of Enterosgel for the patients in both groups)

Group	Examination №	LII	NII	HII	Leukocytes, 10^6/l	% eosinophiles	% band neutrophiles	Erythrocytes, 10^{12}/l	Hb, g/l	ALT, U/l	AST, U/l	General bilirubin, μmol/l	Direct bilirubin, μmol/l
Main	3	2,23±0,99	0,19±0,08	2,78±1,57	5016±1673	0,02±0,02	0,036±0,023	3,76±0,76	116,37±21	72,9±65,1	70,1±52,3	14,1±9,6	3,5±7,3
	4	1,93±0,95	0,2±0,096	2,04±1,04	4968±1420	0,014±0,012	0,027±0,022	3,91±0,85	121,03±22,4	57,1±49,7	54,3±47,1	14,2±10,6	3,72±8,37
Control	3	2,3±1,1	0,31±0,16	2,84±1,92	4491±1396	0,043±0,032	0,06±0,033	4,12±0,55	128,82±16,5	62±48	61±47	11,8±3,7	2,4±1,4

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	2	2,1± 0,99	0,3± 0,12	2,32 ±1,2	422 9±9 67	0,02 9±0, 022	0,05 4±0, 028	3,75 ±0,5 5	127, 82± 19,5 9	53± 40	50± 29,2	12,9 ±3,8 7	3,16 ±1,5 7

Research Materials and Methods

Examined were 69 patients at the age 34 ± 7 years diagnosed with HIV infection who had started receiving HAART drugs. The main (experimental) group included 46 patients (19 women and 27 men), control group – 23 patients (7 women and 16 man). One patient in the main group and three patients in the control group had the second clinical stage of HIV infection (according to WHO classification, 2002), 22 patients in the main group and 17 patients in the control group had the third clinical stage of HIV infection, the fourth clinical stage of HIV was observed in 23 patients in the main and three patients in the control group. Level of CD4 lymphocytes in the main group was 111 ± 137 cells / µl, counter group - 138 ± 104 cells / µl.

In the main group, a traditional therapy of diarrheal and intoxication syndromes was conducted as well as two 2-week courses of Enterosgel: the first - along with start of HAART therapy (within the first two weeks of HAART); the second - 1.5 months after the start of HAART (HAART lasting 7 and 8 weeks), if no adverse reactions (AR) occurred. With the development of AR (diarrhea, nausea, vomiting, rash, intoxication syndrome) the second course of Enterosgel was assigned from the onset of AR. Enterosgel was administered at a dose of one tablespoon 3 times a day 2 hours after meal.

Patients in the control group were only under HAART and traditional therapy. A term of monitoring for both groups of patients was two months.

Rate evaluation in both groups was conducted four times (Fig. 1): at the beginning of HAART, on day 14 of HAART, 1,5 months after beginning of HAART, 2 months after beginning of HAART – in case no AR was observed, and in 2 weeks - in case AR was observed.

Figure 2. Rate of diarrhea syndrome reduction

Figure captions:

Stool normalization

Stool reduction

Control group

Main group

Days from the beginning of diarrhea

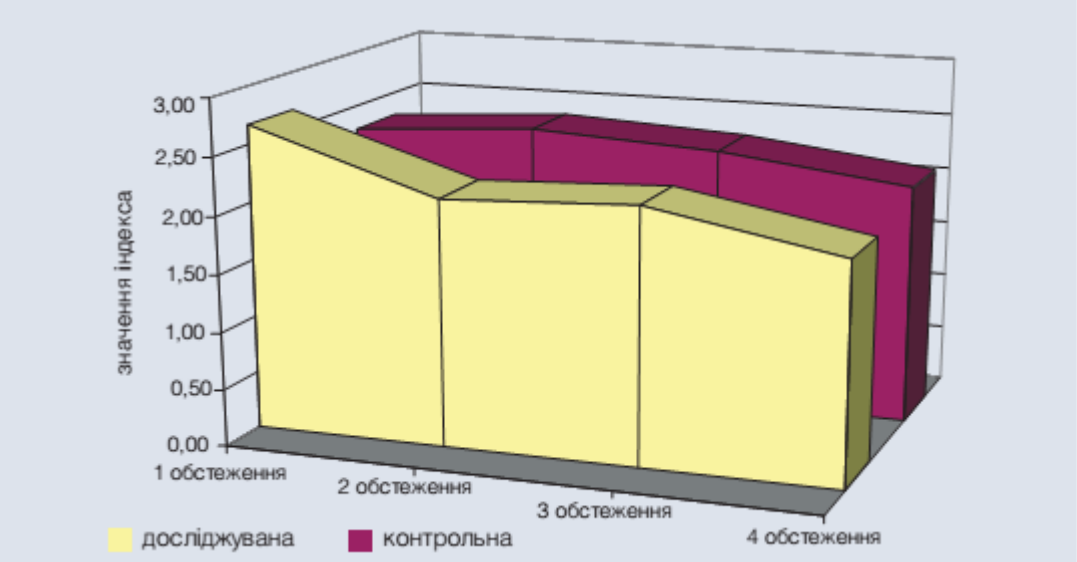

Figure 3. Dynamic pattern of leukocytal intoxication index (average rates)

Figure captions:

Indicator values

1st examination – 2nd examination – 3rd examination – 4th examination

Main Group – control group

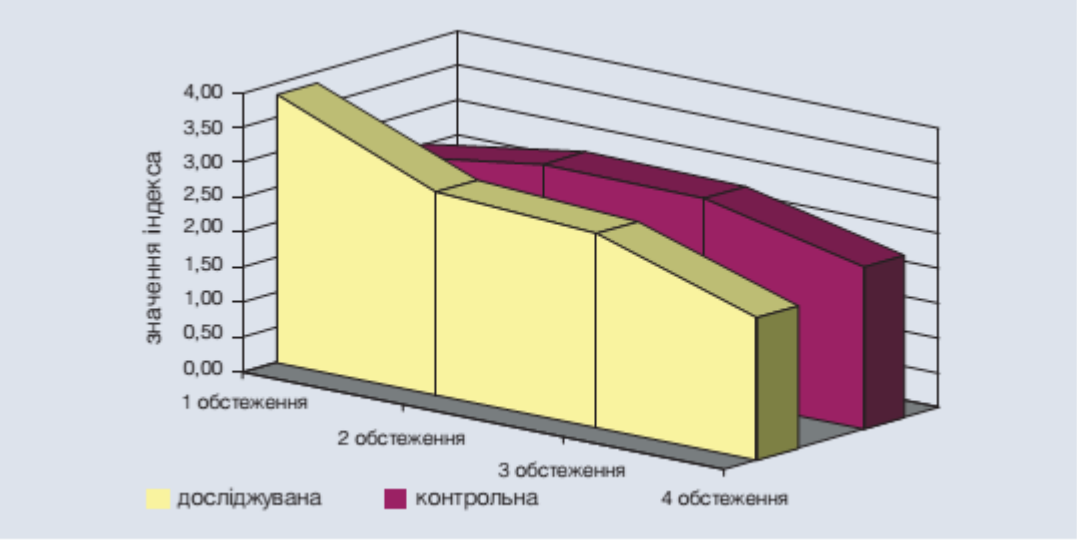

Figure 4. Dynamic pattern of hematological intoxication index (average rates)

Figure captions:

Indicator values

1st examination – 2nd examination – 3rd examination - 4th examination

Main Group – control group

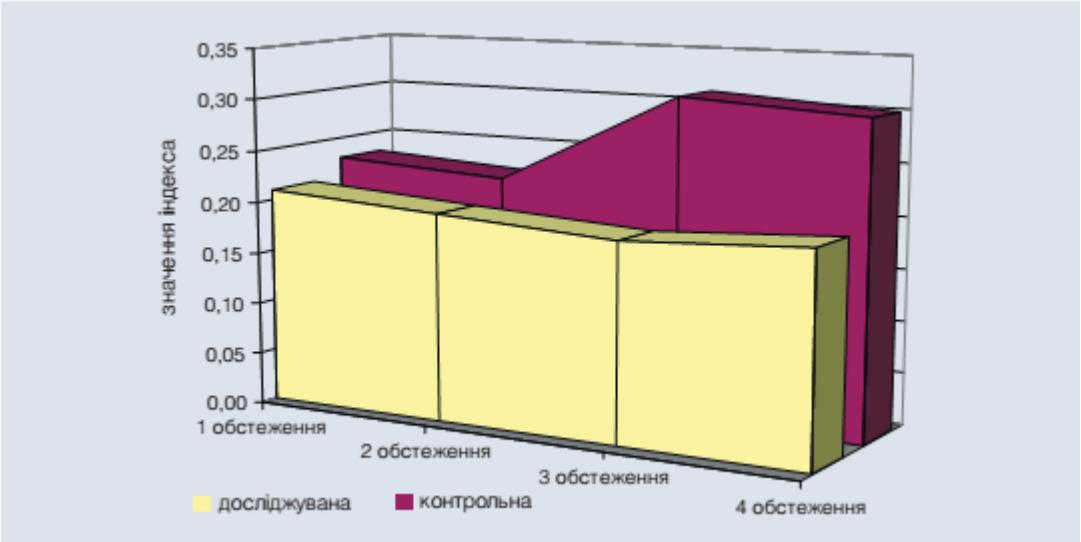

Figure 5. Dynamic pattern of nuclear intoxication index (average rates)

Figure captions:

Indicator values

1st examination – 2nd examination – 3rd examination - 4th examination

Main Group – control group

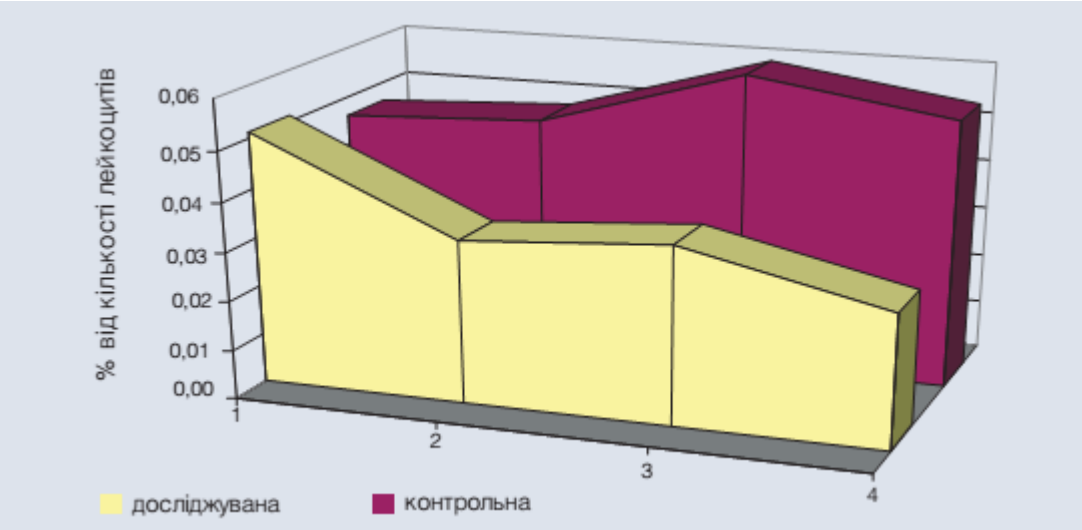

Figure 6. Dynamic pattern of rod nuclear cells in both groups (average rates)

Figure captions:

Indicator values

1st examination – 2nd examination – 3rd examination - 4th examination

Main Group – control group

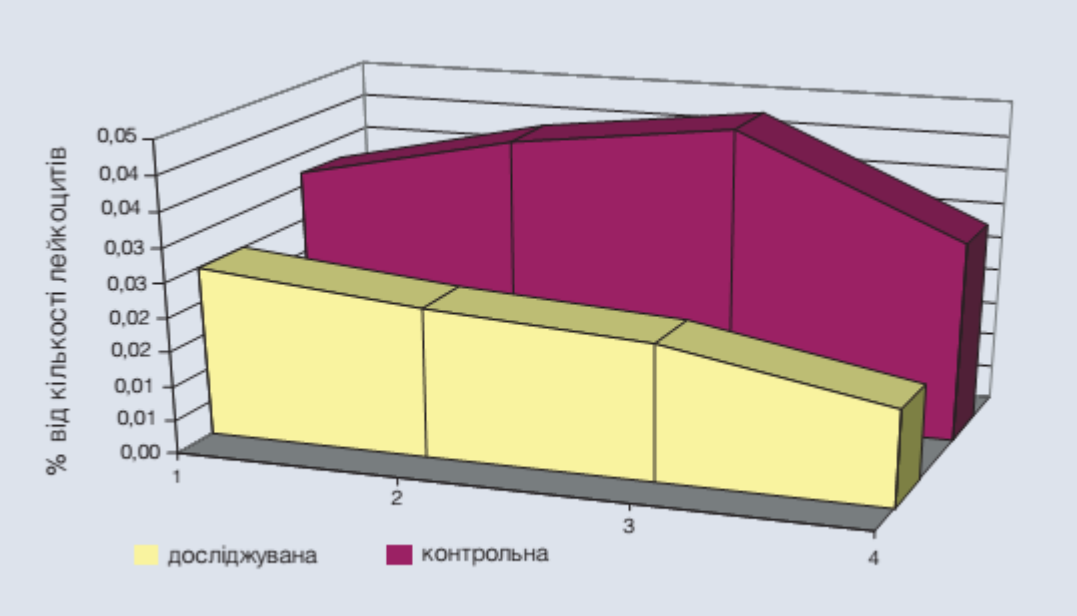

Figure 7. Dynamic pattern of eosinophils in both groups (average rates)

Figure captions:

% of number of leukocytes

1st examination – 2nd examination – 3rd examination - 4th examination

Main Group – control group

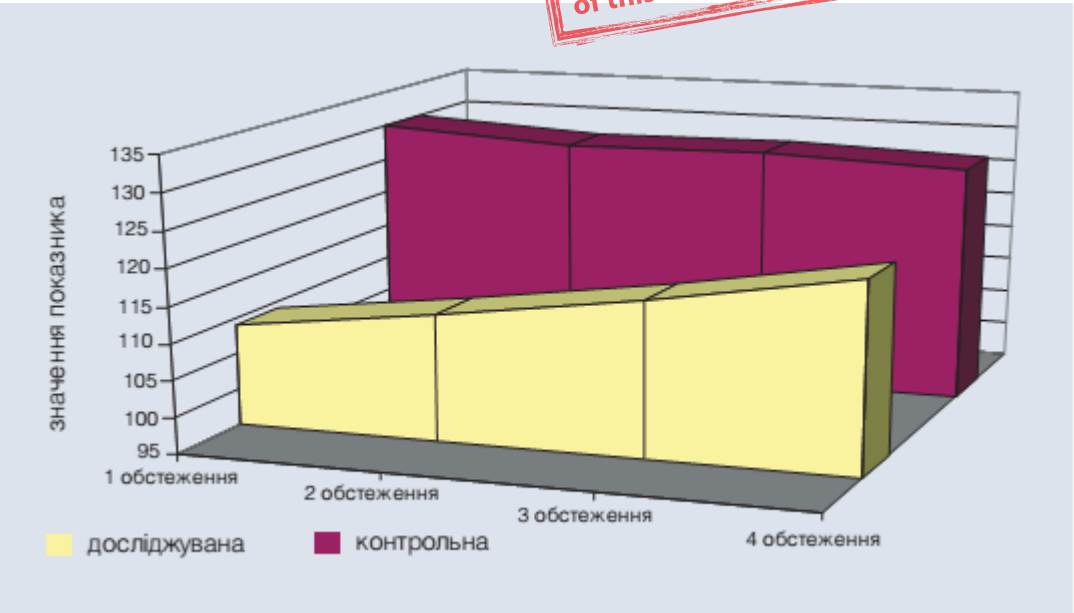

Figure 8. Dynamic pattern of Hb level (average rates, g/l)

Figure captions:

Indicator values

1st examination – 2nd examination – 3rd examination - 4th examination

Main Group – control group

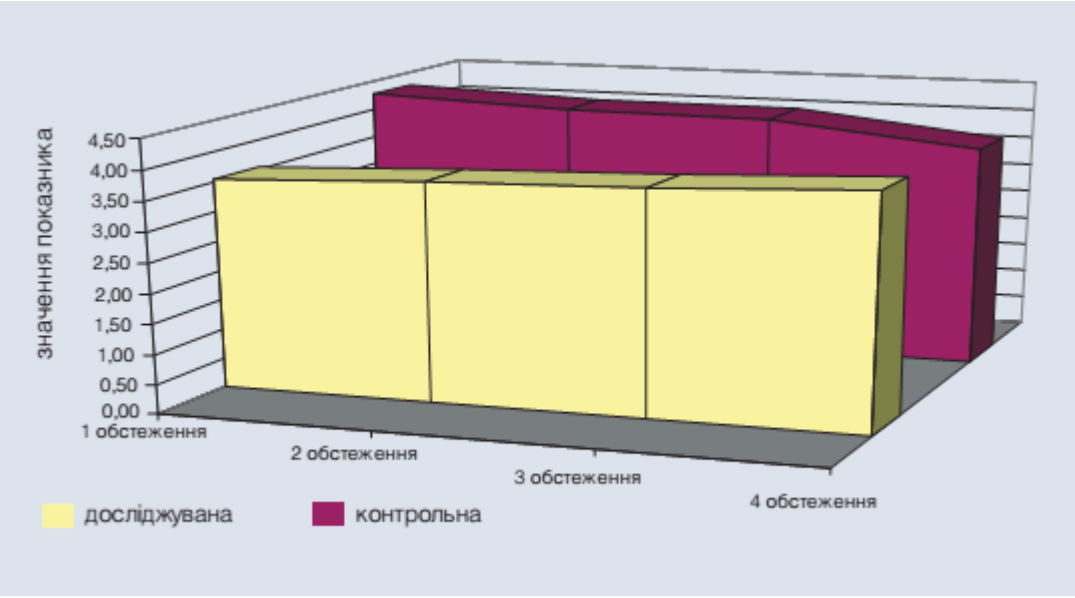

Figure 9. Dynamic pattern of erythrocyte level (average rates, cells x 10^{12}/l)

Figure captions:

Indicator values

1st examination – 2nd examination – 3rd examination - 4th examination

Main Group – control group

Status of the patients was evaluated using the following criteria:

- incidence of AR in patients of main and control groups and AR analysis;
- evaluation of diarrhea syndrome dynamics;
- evaluation of intoxication syndrome for:

Subjective data (patient complaints of weakness, nausea, vomiting, loss of appetite, abdominal pains); as well as laboratory values: endogenous intoxication index – leukocyte intoxication index (LII), nuclear intoxication index (YAII), hematological intoxication index (HII), presence of hemopoietic hypoplasia (hemoglobin and erythrocytes); by the number of rod nuclear cells; presence of eosinophilia.

Results and Discussion

The results are shown in Tables 1, 2 and on the Figures 2-8. All specified numerical values consist of mean value ± standard deviation.

During HAART, adverse reactions occurred in 13 (28%) patients of the main group and in 6 (26%) patients in the control group. Nausea, vomiting, diarrhea was observed in the patients as well as general intoxication manifestations (deterioration of the general sense of well-being, weakness, laxity, headache), anemia, compromised liver function (increased transaminase level), neuropathy, rash.

It has been found that diarrheal syndrome disappeared more quickly in the patients of the group on treatment with Enterosgel. A tendency for reduction of average values of LII, HII, the number of rod nuclear cells, eosinophils, ALT and AST was also observed. NAII levels in patients of the main group practically did not change throughout the observation period, while in the control group YAII significantly increased by the third examination.

Unlike the main group, patients in the control group experienced an increase in the number of rod nuclear cells and eosinophils by the third examination. Levels of erythrocytes and leukocytes did not change significantly.

Side effects of Enterosgel has not been found during the study in HIV-infected patients.

Conclusions

1. Application of Enterosgel enterosorbent in the patients with AIDS in the development of adverse reactions to antiretroviral therapy promotes more rapid reduction of diarrhea and intoxication syndrome (disappearance of subjective complaints, reduction of mean values of intoxication indexes, rod nuclear cells and eosinophils, positive dynamics of reduce of transaminase average level).

2. No adverse reactions caused by Enterosgel has been identified during its application as a part of complex therapy of pathological conditions in HIV-infected patients.

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