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OXIDATIVE STRESS IN HIV INFECTION AND ITS EFFECTS ON THE FEMALE REPRODUCTIVE SYSTEM AND PREGNANCY

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▪ The epidemic situation of HIV infection in the world today remains extremely difficult. In recent years, the virus has been increasingly affecting the so-called prosperous segments of the population. This is confirmed by the increase in the percentage of heterosexual transmission. Thus, in 2019, almost 60% of HIV infections were associated with this type of transmission. The determination of possible differences in the course of the infection by gender has been of interest to researchers from the very beginning of the epidemic. Undoubtedly, there should be differences in the course of the disease in men and women, especially taking into account pregnancy and childbirth in women, and this is the subject of numerous studies in various countries. In the world medical literature, the clinical course of the disease is adequately covered. However, at present, little is known about lipid peroxidation and the activity of the antioxidant blood system in HIV patients, including pregnant women. This article presents a review of the current state of the problem and analyzes studies of free radical oxidation in HIV-infected people. This study was aimed at the analysis and discussion of data on free radical and antioxidant system activities in HIV-infected people, including pregnant women.

▪ **Keywords:** lipid peroxidation; oxidative stress; antioxidants; human immunodeficiency virus; infections; pregnancy.

ОКИСЛИТЕЛЬНЫЙ СТРЕСС ПРИ ВИЧ-ИНФЕКЦИИ И ЕЕ ВЛИЯНИЕ НА ЖЕНСКУЮ РЕПРОДУКТИВНУЮ СИСТЕМУ И БЕРЕМЕННОСТЬ

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▪ Эпидемическая ситуация по ВИЧ-инфекции во всем мире на сегодняшний день остается крайне сложной. В последние годы вирус все больше поражает так называемые социально благополучные слои населения. Это проявляется прежде всего в увеличении доли гетеросексуального пути передачи: в 2019 г. почти 60 % случаев заражения ВИЧ связаны с таким типом передачи. Определение возможных различий в течении данной инфекции по гендерному типу интересует исследователей с самого начала эпидемии. Несомненно, должны существовать различия в проявлении болезни у мужчин и женщин, особенно с учетом беременности и родов у женщин, что является предметом многочисленных исследований в различных странах. Клиническое течение заболевания достаточно хорошо освещено в мировой медицинской литературе, но в настоящее время мало изучены процессы перекисного окисления липидов и активность антиоксидантной системы крови у инфицированных ВИЧ, в том числе отсутствует исчерпывающая информация по изучению липопероксидации у беременных с ВИЧ. В статье представлен обзор современного состояния проблемы, освещен анализ литературы по исследованиям особенностей изменений показателей свободнорадикального окисления у ВИЧ-инфицированных. Цель работы — анализ и обсуждение данных о состоянии показателей свободнорадикального окисления, а также активности антиоксидантной системы у больных ВИЧ-инфекцией, в том числе у беременных.

▪ **Ключевые слова:** перекисное окисление липидов; окислительный стресс; антиоксидантная защита; вирус иммунодефицита человека; инфекции; беременность.

Introduction

Recent decades are witnessing a steady growth in the incidence of socially significant infections in both Russia and other countries [1–5]. More than 1.2 million patients (1,220,659) infected with the human immunodeficiency virus (HIV) are registered in the Russian Federation. About 350,000 of them are women of reproductive age (46.6%), with the prevailing sexual transmission (50.3%). HIV infection is diagnosed in 1.2% of the population aged 15–49 years, and most of the diseases occur in the most active age (35–39 years).

In Russia, the largest number of men with HIV infection was registered at the age of 30–40 years (4%); and HIV was most often registered in women aged 30–35 years (2%–3%) [6]. Figure 1 presents the prevalence of HIV infection in 2019 by the regions of Russia.

The Irkutsk region is one of the most unfavorable regions in terms of the epidemiological situation of HIV infection in the Russian Federation. As of December 2019, 30,114 people infected with the immunodeficiency virus were identified in the Irkutsk region; there were 2,943 new cases, with prevailing sexual transmission (80%). Among the infected patients, 1,531 were women (52.0%) with an average age of 30–39 years [7]. Most of the women with HIV infection are in the active reproductive age. This occurrence is responsible for an increase in the prevalence of pathology among pregnant women, and their share has doubled over the past ten years [8].

The absence of symptoms in the early stages, a long seronegative period, difficulties in diagnosing the disease, and the spread of drug addiction in the Russian Federation render HIV infection as one of the most crucial challenges of modern society.

All of the above challenges indicate that the problem of HIV infection needs an extremely urgent attention. However, among numerous works on various aspects of HIV infection, either in Russia or in other countries, none of them have practically and fully presented the aspects of changes in the parameters of the lipid peroxidation system (LPO) and the activity of the antioxidant defense system in the patients with HIV infection, including pregnant women.

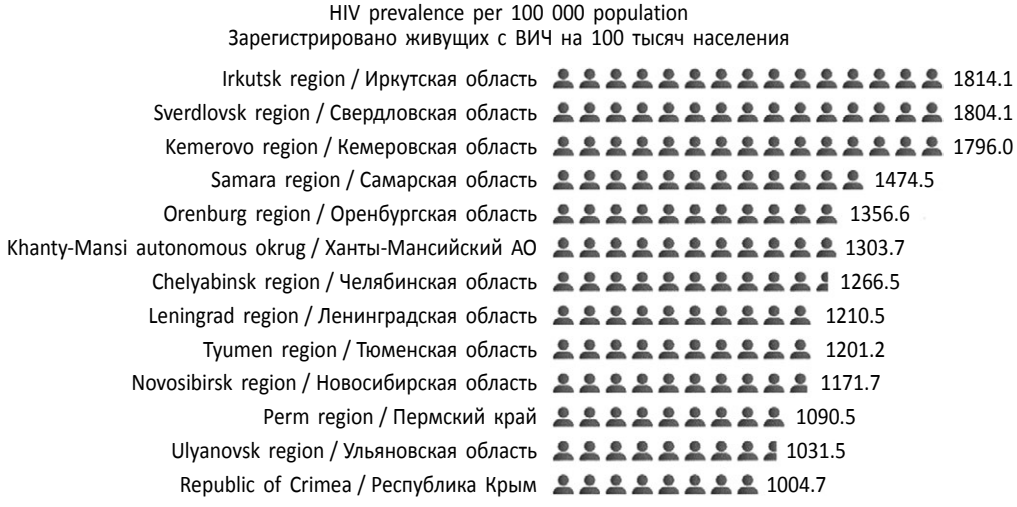
The objective of this review is to analyze the data from international studies on the problem under consideration.

In the review, we investigated the database of the scientific electronic library–eLibrary–for 2010–2020, as well as the full-text and available-for-viewing publications. We also used an English-language database of medical and biological publications created by the National Center for Biotechnology Information to further our search.

We conducted the search using the following keywords: HIV, human immunodeficiency, virus, lipid peroxidation, antioxidant defense, antioxidants, and pregnancy.

HIV infection as a medical and social problem

There has been a continuous and steady growth in the incidence of HIV infection around the world. By the end of 2017, since the beginning of the



Regions of Russia with a high prevalence of HIV infection in 2019 (according to Rospotrebnadzor)

Регионы России с наибольшей распространенностью ВИЧ-инфекции в 2019 г. (по данным Роспотребнадзора)

epidemic, more than 77 million people worldwide (estimated range: 60–100 million) were infected and more than 35 million people (25–50 million) have died from HIV/AIDS-related diseases [9]. The UNAIDS data suggest that the total number of people living with HIV/AIDS in the world amounted to 36.9 million (31.1–43.9 million) by the end of 2017. The majority of these adult patients (35.1 million) were women (18.2 million). Compared to 1990, the prevalence of HIV infection among the global population has grown by almost three times (from 0.3% among the adult population aged 15–49 years to 0.8% in 2017) [10]. The HIV pandemic has become the most destructive one in the human history.

Currently, the following classification of HIV infection is adopted in Russia [11].

Stage I is incubation. The period from the moment of infection until the appearance of signs of acute infection and/or the production of antibodies (from three weeks to three months). At this stage, HIV is multiplying actively, but there are no clinical manifestations yet, and antibodies are not detected.

Stage II is primary manifestations. The active replication of HIV continues. The body's primary response to the intrusion of the pathogen in the form of clinical manifestations and/or the production of antibodies is noted.

The disease can take several forms:

- asymptomatic phase (antibodies are detected, but there are no clinical manifestations; it is the most favorable form in terms of the disease prognosis).
- acute HIV infection without secondary manifestations (registered in 50%–90% of infected patients in the first three months after infection).

The number of CD4 lymphocytes is often decreased transiently, which can cause sore throats, pneumonia, herpes infections, and other diseases (noted in 10%–15% of infected patients). Moreover, the more severe advancement of the acute infection, especially if it was accompanied by secondary diseases, increases the probability of its rapid progression.

Stage III is latent. Immunodeficiency progresses slowly, and the level of CD4 lymphocytes gradually decreases (on average, at a rate of 50–70 cells/μl per year). The virus replicates moderately, and there is minor lymphadenopathy. The stage duration lasts from 2 to 20 years or more (6–7 years on an average).

Stage IV is represented by secondary diseases. The replication of HIV continues, leading to the death of CD4 lymphocytes and the depletion of their population, which, in the presence of immunodeficiency, results in secondary opportunistic diseases.

Stage IVA develops 6–10 years after the moment of infection. Weight loss by no more than 10% is noted, as well as fungal, viral, and bacterial lesions of the skin and mucous membranes, shingles, repeated pharyngitis, sinusitis (the number of CD4 lymphocytes is reduced to 350–500 cells/μl). Phases include progression (with or without antiretroviral therapy) and remission (spontaneous, after previous antiretroviral therapy, during antiretroviral therapy).

Stage IVB develops 7–10 years after the moment of infection (the number of CD4 lymphocytes is reduced to 200–350 cells/μl). Phases include progression and remission.

Stage IVC develops 10–12 years after the moment of infection (the number of CD4 lymphocytes is less than 200 cells/μl). Phases include progression and remission.

Stage V is terminal. Acute infection is mainly associated with a high viral load.

In the Russian Federation, the main method of laboratory diagnostics of HIV infection is the detection of antibodies against the virus using enzyme immunoassay. Immunoblotting is also used (the specificity of the results is tested by the detection of antibodies to certain proteins of the virus) for the same objective.

The polymerase chain reaction method is used to predict the course of the disease, assess the severity of HIV infection during vaccination, adjust the therapy, determine the virus subtype in the population, compare the virus subtype with the clinical course of the disease, and determine the levels of CD4 lymphocytes (determination of the viral load, which is the number of copies of HIV RNA in plasma).

By using the total number of lymphocytes, T helpers (CD4), T suppressors (CD8), and the immunocorrecting index (ratio of CD4/CD8), immunological methods assist in establishing the stage of the disease.

The widespread prevalence of the virus has exerted a detrimental effect on the general psychological state of society. HIV infection both in Russia and throughout the world ranks first in terms of psychological stress [10, 12]. Many people have a poor understanding of what HIV infection is and the way it is transmitted. They view people with HIV infection as a threat to themselves and their family members. People who are in fear due to their own ignorance unreasonably persecute people with HIV infection. Moreover, people with HIV infection are also in a state of excitement and nervousness, and transfer this condition to other poorly informed people. The highest rates of development of the HIV epidemic are registered in Russia. Nevertheless, tens of millions of people around the world are already living with HIV while being surrounded by hundreds of millions of relatives and friends. The diagnosis of HIV infection is accompanied by many social and psychological problems that appear long before a person may require medical care.

Several authors have suggested that almost 90% of the newly diagnosed cases of HIV infection are injectable drug users [11, 13, 14]. The spread of the virus among drug addicts not only contributes to an increase in the incidence of HIV infection, but also aggravates its course. Along with the basic, pathogenic properties of the virus and the ability of the immune system to resist it, there are many concomitant factors that determine the aspects of certain links of pathogenesis [13]. A few other researchers have shown that some of these factors include the ways and means of HIV transmission, the combination of viral hepatitis and HIV, along with the combination of tuberculosis and HIV [15–19]. It is known that the reactions of nonspecific resistance of the organism form the basis of immunity toward infectious agents [10]. Therefore, a combination of cellular and humoral factors creates the antimicrobial protection. The background state of nonspecific resistance of the organism largely determines the development and outcome of any infectious process. Neutrophilic granulocytes provide the first line of antimicrobial defense, and the course and outcome of the inflammatory process largely depend on their functional potential [20].

The State Strategy for Counteracting the Spread of HIV Infection in the Russian Federation for the period up to 2020 and beyond was approved in 2016. The following areas have been identified as the main target indicators for the implementation of the strategy:

- raising the awareness of the citizens of the Russian Federation on HIV infection issues, as well as creating a social environment that excludes discrimination against persons with HIV infection; development and implementation of interdepartmental programs for the prevention of HIV infection; to work in key population groups and facilitate the involvement of socially oriented nonprofit organizations in the implementation of these programs.
- ensuring a comprehensive interdisciplinary approach in the provision of medical care and social support for the people with HIV infection, including an increase in the coverage of the population with medical examination for HIV infection; provision of antiretroviral therapy for patients with HIV infection, further reducing the risk of HIV transmission from mother to child; development and introduction of technologies for the social adaptation and rehabilitation of patients with HIV infection, as well as measures for their social support.
- improvement of epidemiological control and surveillance of the spread of HIV infection in the Russian Federation based on the scientifically grounded approaches to conduct the epidemiological monitoring of HIV infection.

HIV infection in pregnant women

The protection of mothers and children in the context of the HIV epidemic in all the regions of the world, considering geographical, epidemiological, social, and other characteristics, has become one of the most significant challenges in medicine in the recent years.

Transmission of HIV from an infected mother to her child can occur:

- antenatally (transplacentally through the amniotic membranes and amniotic fluid during diagnostic invasive procedures);
- intranatally (during childbirth); and
- postnatally (during breastfeeding) [21].

The factors contributing to mother-to-child transmission of the virus are complex and diverse. The transmission of infection is facilitated by various pathological conditions of the mother and fetus, an impairment of the placenta protective

function, and the peculiarities of the course of labor. Generally, the state of health of the mother is certainly important. The use of drugs, alcohol, uncontrolled sexual behavior during pregnancy, malnutrition, and others have a negative effect on HIV transmission. The risk of perinatal infection increases with the acute stage of HIV infection and the progression of the disease with high viremia (more than 10,000 copies/μl). More than half of women transmit the infection with a viral load of more than 50,000 copies/μl. The mother's risk of contracting HIV increases with a decrease in the number of CD4 lymphocytes in the blood (less than 500 cells/μl), as well as with extragenital pathology (diseases of kidneys or the cardiovascular system, diabetes mellitus) and sexually transmitted diseases [22, 23]. There was a correlation of an increased transmission of HIV with chorioamnionitis, placental insufficiency, and a premature separation of placenta and bleeding. It has been established that HIV infection can cause preterm birth with antenatal infection [24, 25]. Due to the immaturity of the immune system, a premature baby is also at a greater risk during labor. The disruption of continuity of the skin and mucous membranes of the newborn becomes an additional risk factor.

The examinations of pregnant women confirm the active involvement of women of reproductive age in the HIV epidemic [26–28]. Among pregnant people with HIV infection who have not received highly active antiretroviral therapy, there is an increased incidence of obstetric complications, childbirth, and adverse outcomes in children (premature birth, low birth weight). A prospective study showed that the frequency of spontaneous miscarriages in pregnant women with HIV infection was significantly higher than in a group of healthy women [29], thereby indicating a negative impact of HIV.

Other data indicate that HIV infection, along with social status, significantly affect the formation of intrauterine fetal hypoxia, weight, and the APGAR score. The combination of HIV infection and social status mutually increases the negative effect, and the worst results were recorded in the socially unadapted women with HIV infection. The three-stage antiretroviral prophylaxis significantly reduces the vertical transmission of HIV from mother to fetus [15].

Antiretroviral therapy and chemoprophylaxis during pregnancy and childbirth significantly reduce the risk of perinatal HIV transmission [22, 30]. However, to date, there are no antiretroviral drugs without side effects. Due to the large doses of drugs and the duration of therapy, the more or less pronounced side effects of antiretroviral therapy and chemoprophylaxis are registered in almost all the female patients (during the first weeks) [31].

The use of antiretroviral drugs by pregnant women with HIV infection causes certain changes in the hemostatic system [31]; however, hypocoagulation shifts are more often registered in these women. The authors associate the development of coagulopathy with a disorder of the synthesizing function of the liver, a reduced formation of blood coagulation factors, and an excessive activity of the fibrinolytic system. The targeted preoperative preparation of pregnant women with HIV infection helps in neutralizing the newly appearing manifestations. These studies demonstrate the feasibility of selecting the alternative chemoprophylaxis regimens.

Among the complications of pregnancy, placental insufficiency is registered in 35% of women with HIV infection. At the same time, there is a paucity of research on the issues of the placental barrier, which act as an important defense mechanism that prevents the transmission of the virus from the mother to the fetus [25].

Thus, on the territory of Russia, there is an increasing feminization of the HIV epidemic, which is annually leading to an increase in the number of pregnant women with HIV infection and the birth of children with perinatal exposure. Over the past ten years, there are an increased proportion of pregnant women with HIV infection and with an established diagnosis before pregnancy and who wish to give birth [30]. This tendency arises from the conscious decision of women to receive three-stage antiretroviral therapy and the desire to reduce the risk of vertical transmission of HIV infection to future children.

The state of the lipid peroxidation system and the activity of the antioxidant defense of the blood in the patients with HIV infection

For many years, the role of reactive oxygen species and the free radical processes initiated by them in various pathological conditions has been widely

discussed. Under normal conditions, the activity of these processes is low. However, under stressful situations, there is an increased formation of reactive oxygen species. Under the influence of these situations, an excessive and uncontrolled activation of LPO processes occurs, which ultimately can result in a pathological condition that is accompanied by an imbalance of enzymatic and nonenzymatic components of the antioxidant defense system.

The intensification of LPO processes is a characteristic manifestation of oxidative stress, which is indicated by an increase in the content of its products. Information on the content of LPO products in the biological media can provide information on the depth and extent of the pathological process. Compounds such as diene conjugates, as well as one of its end products, malondialdehyde (MDA), act as the markers of LPO processes. Antioxidant enzymes are represented as a special object of damage in HIV infection because a disorder of their activity indirectly indicates a significant restructuring of the modes of vital activity of cells, metabolic rate, as well as activation and inactivation of a number of biologically active substances.

Currently, a number of studies have been conducted to investigate the state of the LPO system and the activity of antioxidant blood defense in various diseases [32–39], including HIV infection [40–46]. However, there are few data on the investigation of the parameters of the LPO–AOD system (antioxidant defense system) in the pregnant women with HIV infection [47, 48].

In a study of the blood serum of patients with HIV infection [40], the authors revealed that the prooxidant reactions already predominate in the earliest stages of the disease (during the period of asymptomatic HIV carriage) and also identified the laboratory signs of oxidative modification of lipoprotein complexes.

A special role in both the activation of LPO processes and the pathogenesis of impaired activity of antioxidant defense enzymes is assigned to the HIV itself. V.V. Kostyushov et al. revealed that the specific immune interaction of antigen and antibody, including HIV antigen with HIV antibodies, is accompanied *in vitro* by a significant disorder of the thiol-disulfide redox system [40]. During these reactions, the low molecular weight disulfides, both symmetric and mixed, are reduced; thereby resulting in the release of low molecular weight thiols (R–SH forms). These processes may be associated with the activation of free radical oxidation and disruption of the activity of AOD enzymes in HIV infection. Peroxide processes are also based on the nonenzymatic redox reactions including the reduced forms of low molecular weight thiols, which can regulate the free radical processes of pro- and antioxidants. The AOD enzymes (superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, etc.) either belong to thiol enzymes or require the presence of thiols for catalytic activity. During the catalyzed reactions, these enzymes use actively free the SH groups of glutathione. Moreover, glutathione is additionally consumed during redox reactions because it acts as a supplier of SH groups, which protect the cells from the OH radical.

The impairment of the activity of AOD enzymes is of great importance in the formation of oxidative stress in the case of HIV infection. LPO activation in HIV is accompanied not only by an increase in the concentration of one of the toxic products of the peroxide cascade, MDA, but also by the oxidative modification of lipoprotein complexes, as well as suppression of the activity of the blood serum antioxidant system enzymes (superoxide dismutase, catalase, glutathione peroxidase). Under these conditions, glutathione reductase demonstrates a major significance.

The authors note that in the manifested forms of AIDS, an increase in the MDA levels is more pronounced, along with an oxidative modification of lipoprotein complexes and impaired activity of AOD enzymes [40]. The detected disorders indicate a molecular imbalance of the serum prooxidant/antioxidant systems, which should be considered while clarifying the clinical stage of the disease and developing a strategy for prescribing antioxidants in their complex preventive and therapeutic use in HIV infection.

Data from other studies also confirm the intensification of LPO processes in HIV infection [49–51]. In the patients with HIV infection at the stage of secondary manifestations, a pronounced activation of LPO processes is noted, as evidenced by a significant increase in the level of highly toxic MDA. There was also a tendency toward the growth of the primary lipid peroxidation products–ketodienes. Significant changes in the AOD system were revealed in the intensification of peroxide

processes at the stage of secondary diseases. The concentration of ceruloplasmin, the activity of erythrocyte catalase [51], and the level of general antioxidant activity [49] were significantly reduced in the patients, thus indicating the depletion of the AOD system.

In a study of the parameters of lipid peroxidation and AOD in the women of fertile age with chronic viral hepatitis (CVH) in combination with HIV infection, as compared to the patients with CVH monoinfection, a higher content of LPO products was noted, along with the decrease in the indicators of general antioxidant activity, superoxide dismutase activity, as well as the concentration of fat-soluble vitamins [19]. This result suggests that the presence of coinfection (CVH in combination with HIV) is characterized by a more intense lipid peroxidation processes and a more pronounced deficiency of antioxidant factors than with CVH monoinfection.

The study of the characteristics of changes in the lipid peroxidation parameters, AOD, as well as the state of the reproductive system in women of fertile age with monoinfection (HIV) and coinfection (HIV and hepatitis B and/or C), revealed that the indicators of patients with HIV monoinfection along with the values of primary and secondary LPO products are increased with a reduced antioxidant activity in the group with HIV coinfection, as compared with the control values. The incidence of luteal phase failure is increased in the case of concomitant infection in the women with HIV infection [27]. Thus, if HIV is accompanied by another infection, then oxidative stress and deficiency of antioxidant factors are more pronounced, and the incidence of luteal phase deficiency is increased, thereby confirming the aggressive influence of HIV on the functional state of cells.

A comprehensive study of LPO parameters and the blood AOD system of patients with HIV infection, depending on the stage, the intensity of the pathological process, the presence of drug addiction, concomitant infection, and exacerbation of other diseases, also revealed the activation of lipid peroxidation processes during the decrease in the body's antioxidant defense [52].

The effect of oxidative stress on the female reproductive system is widely covered in the literature [53–57] and is beyond doubt. The study of the LPO–AOD system during pregnancy also holds an important scientific interest, especially in the case of complications from various infections, particularly in HIV.

Physiological pregnancy can be accompanied by significant changes in pro- and antioxidant status. During gestation, from the moment of conception to the end of childbirth, integrative processes occur in the mother's body, which are necessary for maintaining the functional unity of the mother's body and the fetus. These processes enable the conduct of the main task, which is the preservation of fetus.

One of the reasons for the increase in the number of free radicals during pregnancy is their participation in the synthesis of progesterone. They activate the LPO process that results in the formation of cholesterol hydroperoxides, which are the precursors of this hormone. Progesterone is a very important hormone that is required to maintain pregnancy. It prepares the uterus endometrium for the implantation of a fertilized ovum and, then, contributes in the maintenance of pregnancy [58].

The literature has shown that an increase in LPO products in trimester III of pregnancy is due to the inhibition of enzymatic and nonenzymatic mechanisms of antiperoxide defense. Simultaneously, there is a decreased activity of catalase [59] and ceruloplasmin [60], which also has ferroxidase activity and inhibits the superoxide anion–radical, excessively leading to the intensification of LPO processes.

The intensification of LPO processes in the blood of pregnant women can be caused by various factors. For example, an excessive intake of iron preparations increases the level of free radicals because any antioxidant under certain conditions can act as a prooxidant and initiate the oxidative processes [61]. At the same time, iron deficiency contributes to the development of iron deficiency anemia, which causes tissue hypoxia. Stress can also have a powerful effect on the activation of LPO processes. In unfavorable life situations, the increased quantities of stress hormones, such as adrenaline and cortisol, are produced, thereby disrupting the normal functioning of the cell that instantly leads to the accumulation and spread of free radicals throughout the body.

The study of pathological conditions at the cellular level in clinical medicine, particularly struc-

tural and functional changes in the cell membranes, along with LPO parameters and AOD activity allows the targeted regulation of free radical oxidation.

Conclusion

Contemporary science and clinical practice offer strong evidence that one of the components of the etiology and pathogenesis of many human diseases is the excessive activation of lipid peroxidation processes. HIV infection is no exception. It affects the decrease in AOD and leads to the intensification of LPO processes, which was substantiated by the conducted studies. Considering the certain specificity of lipids and their constituent longchain fatty acids containing several double bonds, it is not surprising that the LPO system is activated under the influence of exogenous and endogenous factors, further leading to various negative consequences.

The HIV epidemic in Russia is a part of the global pandemic. The urgency of the problem for our country is determined by the lack of stabilization of the epidemic process and a steady increase in the number of newly registered cases.

Undoubtedly, a comprehensive study of the complex pathogenetic mechanisms of nonspecific resistance of the organism, as well as the elucidation of the role and significance of indicators of free radical oxidation and AOD in HIV infection, including in pregnant women, is of a strong and considerable interest.

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