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CHANGES IN HUMORAL IMMUNITY AMONG INDIVIDUALS WITH EARLY-STAGE HIV INFECTION

The present study aimed to comprehensively assess humoral immune parameters and cytokine status in individuals newly diagnosed with HIV infection. A total of 783 patients were examined, and serum immunoglobulin profiling was performed in 90 of them. Quantification of IgA, IgM, IgG, IgE, and cytokines (IL-1β, IL-6, IL-4, IL-10) was carried out using ELISA.

Compared with healthy controls, patients with early-stage HIV infection demonstrated pronounced dysregulation of humoral immunity. Serum IgA, IgM, and IgG levels were significantly elevated (1.95-fold, 1.51-fold, and 2.46-fold increases, respectively), indicating activation of both local and systemic immune responses. Despite this enhancement, the heterogeneity in magnitude of change suggests strain on the primary immune response and an insufficient secondary response. Strikingly, IgE concentrations increased 84.88-fold, pointing to a highly sensitized allergic background likely driven by opportunistic infections accompanied by secondary immunodeficiency.

Similarly, cytokine levels were markedly increased. Pro-inflammatory cytokines showed differential enhancement: IL-1β levels rose 5.75-fold, while IL-6 increased 1.50-fold, suggesting a dominant role of IL-1β in inflammatory signaling and antiviral immunity. Anti-inflammatory cytokines also increased significantly: IL-4 by 6.21-fold and IL-10 by 1.94-fold. This imbalance between pro- and anti-inflammatory mediators reflects complex immune dysregulation associated with early HIV infection.

Overall, these findings demonstrate substantial activation yet imbalance of humoral immunity in primary HIV infection. The coexistence of heightened immunoglobulin and cytokine synthesis, excessive IgE production, and insufficient secondary immune response indicates an early breakdown in coordinated immune regulation. These results provide important insights for monitoring immune dysfunction and improving clinical management during early stages of HIV.

Keywords: HIV infection, humoral immunity, cytokines, immune dysregulation, immunoglobulins, IL-1β, IgE

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АИТВ-инфекциясының ерте сатысындағы тұлғалардың гуморальды иммунитетіндегі өзгерістер

Бұл зерттеудің мақсаты – алғаш анықталған АИТВ-жұқпасы бар тұлғаларда гуморальды иммунитет көрсеткіштері мен цитокиндік мәртебені кешенді бағалау. Барлығы 783 пациент зерттелді; олардың 90-ында иммуноглобулин деңгейлері анықталды. Қан сарысуындағы IgA, IgM, IgG, IgE және IL-1β, IL-6, IL-4, IL-10 цитокиндерінің концентрациялары ИФТ әдісімен өлшенді.

Сау адамдармен салыстырғанда АИТВ-жұқпасының ерте сатысындағы науқастарда гуморальды иммунитеттің айқын дисрегуляциясы анықталды. IgA, IgM және IgG деңгейлері тиісінше 1,95; 1,51 және 2,46 есе жоғары болды, бұл жергілікті және жүйелік иммундық жауаптың күшеюін көрсетеді. Өзгерістер қарқындылығының әркелкілігі бастапқы иммундық жауаптың әлсіреуін және қайталама иммундық жауаптың жеткіліксіздігін сипаттайды. Ерекше назар аударатын жайт – IgE деңгейінің 84,88 есеге артуы, бұл екіншілік иммунтапшылық жағдайында дамитын оппортунистік инфекциялармен байланысты айқын аллергиялық фонның қалыптасуын көрсетеді.

Сонымен қатар цитокиндердің айтарлықтай жоғарылағандығы анықталды. Қабыну медиаторларының ішінде IL-1β деңгейінің 5,75 есеге, IL-6 деңгейінің 1,50 есеге өсуі тіркелді, бұл IL-1β-дің қабыну мен вирусқа қарсы иммунитеттің қалыптасуындағы басым рөлін көрсетеді. Қабынуға қарсы цитокиндер – IL-4 (6,21 есе) және IL-10 (1,94 есе) концентрациялары да артты, бұл иммундық дисрегуляцияның күрделі сипатын айқындайды.

Жалпы алғанда, АИТВ-жұқпасының бастапқы кезеңінде гуморальды иммунитеттің айқын белсенуімен қатар оның теңгерімсіздігі байқалды. IgE деңгейінің күрт артуы, цитокин синтезінің күшеюі және қайталама иммундық жауаптың жеткіліксіздігі иммундық реттелудің ерте бұзылуын көрсетеді. Алынған деректер иммундық өзгерістерді бақылау және АИТВ-жұқпасының ерте кезеңінде клиникалық басқаруды жақсарту үшін маңызды.

Түйін сөздер: АИТВ-жұқпасы, гуморальды иммунитет, цитокиндер, иммундық дисрегуляция, иммуноглобулиндер, IL-1β, IgE.

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Изменения гуморального иммунитета у лиц с ранней стадией ВИЧ-инфекции

Целью настоящего исследования была комплексная оценка показателей гуморального иммунитета и цитокинового статуса у лиц с впервые диагностированной ВИЧ-инфекцией. Всего обследованы 783 пациента; у 90 из них проведено определение уровней иммуноглобулинов. Количественное определение IgA, IgM, IgG, IgE, а также цитокинов (IL-1β, IL-6, IL-4, IL-10) в сыворотке крови осуществляли методом ИФА.

По сравнению со здоровыми лицами у пациентов с ранней стадией ВИЧ-инфекции выявлена выраженная дисрегуляция гуморального иммунитета. Уровни IgA, IgM и IgG были значительно повышены (в 1,95; 1,51 и 2,46 раза, соответственно), что указывает на активацию местного и системного иммунного ответа. При этом неодинаковая выраженность изменений отражает напряжённость первичного иммунного ответа и недостаточность вторичного ответа. Особенно значимым оказалось увеличение концентрации IgE – в 84,88 раза, что указывает на выраженный аллергический фон, вероятно формируемый на фоне вторичного иммунодефицита и развития оппортунистических инфекций.

Также обнаружено существенное повышение уровня цитокинов. Среди провоспалительных медиаторов отмечено доминирование IL-1β, концентрация которого увеличилась в 5,75 раза, тогда как IL-6 – в 1,50 раза, что подтверждает более значимую роль IL-1β в развитии воспаления и противовирусного иммунитета. Уровни противовоспалительных цитокинов также возрастали: IL-4 – в 6,21 раза, IL-10 – в 1,94 раза, что отражает комплексный характер иммунной дисрегуляции.

Таким образом, в ранней фазе ВИЧ-инфекции наблюдается существенная активация, но одновременно и дисбаланс гуморального иммунитета. Резкое повышение IgE, усиление синтеза цитокинов и недостаточный вторичный иммунный ответ свидетельствуют о раннем нарушении регуляции иммунной системы. Полученные данные важны для мониторинга иммунных нарушений и улучшения клинического ведения пациентов на ранних этапах ВИЧ-инфекции.

Ключевые слова: ВИЧ-инфекция, гуморальный иммунитет, цитокины, иммунная дисрегуляция, иммуноглобулины, IL-1β, IgE.

Introduction

A decline in the activity of the immune system (secondary immunodeficiency) leads to a reduced ability to combat infections, the emergence of opportunistic infections, and a weakened defense against tumors [1-3].

HIV infection is a slowly progressing pathological condition caused by a virus from the Retroviridae family, genus Lentivirus [4-7]. Once inside the body, the virus targets T-helper/inducer cells that express CD4+ receptors on their surface. HIV can also infect monocytes, macrophages, Langerhans cells, dendritic cells, and microglial cells that possess these receptors [8-10].

Damage to these immunocompetent cells results in decreased immune system activity, ultimately leading to the development of acquired immunodeficiency syndrome (AIDS). CD4+ cells play a crucial role in the immune response by transmitting antigen-related information to B-lymphocytes, promoting their differentiation into plasma cells, and facilitating antibody synthesis [11-13]. This highlights the significance of CD4+ cells in immune regulation [5, 14-15].

Although extensive research has been conducted by both domestic and international scientists on the etiology, progression, pathogenesis, transmission routes, early diagnosis, antiretroviral therapy, and prevention of HIV infection, studies focusing

on immune system function, its alterations, and age-related characteristics remain limited and fragmented [16-17].

The aim of the study was to examine and evaluate the immune status of individuals newly diagnosed with HIV infection.

Materials and methods

For the purpose of conducting the study, blood sera of a total of 783 individuals with primary HIV infection were examined. Of these, 59.51±1.75% (n=466) were men, while 40.49±1.75% (n=317) were women. It is noteworthy that men were significantly ($P<0.05$) more prevalent than women.

12.39±1.18% (n=97) of individuals with HIV infection were permanent urban residents, while 87.61±1.18% (n=686) were permanent rural residents. The higher prevalence of HIV infection among the rural population is attributed to the large number of labor migrants working in various countries. The study revealed that 73.95±1.57% (n=579) of the participants were married, while the remaining 26.05±1.57% (n=204) were unmarried individuals.

It was determined that the majority of those diagnosed with HIV infection were citizens aged 31-40 years (39.08±1.74%) and 41-50 years (33.46±1.69%). The least common age group was 21-30 years old (11.24±1.13%). The fact that the majority of labor migrants fall within this age range (31-50 years) is characterized by a high prevalence of this infection among them.

An apparatus manufactured in 2022 (MR-96A Mindray Co.Ltd, China) was used to perform enzyme-linked immunosorbent assay (ELISA) on blood serum samples from HIV-infected individuals. The concentration of IgA was determined using test kits from Vector Best LLC (Novosibirsk, Russian Federation), while the levels of IgM, IgG, and IgE were measured using test kits from XEMA LLC (Moscow, Russian Federation).

Test kits from "Vector-Best" LLC (Novosibirsk, Russian Federation) were used to determine the concentration of cytokines. These kits were used to measure the concentrations of IL-1β, IL-4, IL-6, and IL-10 in blood serum. The tests were conducted according to the instructions provided with the test kits.

Statistical processing of the obtained materials was carried out using traditional methods of variational statistics, utilizing the "Excel" program. The statistical analysis was performed on a personal computer with a Pentium IV processor, employing a software package designed for medical and biological research.

Results and discussion

Medical records of individuals aged 21-60 years with primary HIV infection were examined. Among these, the concentration of immunoglobulins in blood serum was determined for 90 subjects.

The study evaluated the degree of changes in the concentrations of IgA, IgM, IgG, and IgE in blood serum. For a comparative assessment of the obtained results, 20 healthy individuals were also examined (Table 1).

As shown in Table 1, changes in the concentrations of immunoglobulins in blood serum were observed, revealing a quantitative imbalance. Both the trends and intensities of these changes varied.

Table 1 – Results of studying humoral immunity parameters in individuals with primary HIV infection

Parameters	Healthy individuals, n=20	HIV-infected persons, n=90
IgA, g/l	1,26±0,15	2,46±0,06* ↑
IgM, g/l	1,32±0,14	1,99±0,09* ↑
IgG, g/l	13,53±0,89	33,22±0,06* ↑
IgE, IU/ml	0,64±0,06	54,32±3,20* ↑

Note: * – sign of reliable difference in relation to healthy individuals; ↑ – direction of change.

Considering that IgA, particularly in its secretory form (sIgA), is the primary protein responsible for local, humoral immunity and serves as the «first line of defense» in the body's resistance on mucosal surfaces and in biological fluids, and is frequently found in secretions on mucosal surfaces, it becomes evident that its concentration in the blood is dependent on the state of local immunity, the quantity of antigens entering the body, and the intensity of their entry into the organism.

The study conducted revealed that the IgA level in the blood serum of individuals with primary HIV infection was significantly higher, by 1.95 times, compared to that of healthy individuals – 2.46±0.06 g/l versus 1.26±0.15 g/l, respectively ($P<0.001$). Such an increase in IgA levels indicates enhanced synthesis resulting from the increased strain on local immunity resistance factors.

IgM stands out among all immunoglobulins for being a pentamer, having a large molecular mass, and primarily providing the primary immune response. When an antigen enters the organism, IgM is synthesized first, and its concentration reaches a maximum in blood serum. After 5-6 days, it begins to decrease quantitatively.

In the study, the serum concentration of IgM in the examined pathology was 1.99±0.09 g/l, which was significantly higher by 1.51 times compared to the same indicator in healthy individuals (1.32±0.14 g/l) ($P<0.05$). The tendency of IgM increase was similar to the previously mentioned immunoglobulin; however, the intensity of changes was relatively low. This condition is associated with the low strength of the primary immune response despite a high viral load on local immunity. In our opinion, due to the damage to T-helpers/inducers, which are the «targets» of HIV infection, information about the virus does not fully reach B-lymphocytes, resulting in insufficient synthesis of IgM, which is responsible for the primary immune response.

Considering that IgG has the smallest molecular mass among all immunoglobulins, is the only immunoglobulin that can cross the placenta, constitutes 75% of all immunoglobulins, and primarily provides a secondary immune response, we can understand its crucial importance for the functioning of the immune system. The coating of the antigen surface with IgG molecules (opsonization) enables phagocytes to quickly recognize, engulf, and eliminate them. Additionally, it contributes to the elimination of antigens by activating the complement system through the classical pathway.

According to the results obtained in the study, it was found that the concentration of primary HIV infection in blood serum significantly increased by 2.46 times, unlike the levels of IgA and IgM – 23.22±0.06 g/l compared to 13.53±0.89 g/l, respectively ($P<0.001$). Such an enhancement of humoral immunity is undoubtedly associated with a quantitative deficit of immunocompetent cells, since humoral immunity is part of the overall immune system and is closely interconnected with other components.

The observed quantitative imbalance in the intensity of changes among the studied IgA, IgM, and IgG was indeed attributed to negative alterations in immune system function, strain on this system, and issues in the formation and development of both primary and secondary immune responses.

Along with the immunoglobulins mentioned above, the concentration of IgE in blood serum was also studied. Considering that IgE causes the release of inflammatory mediators into the bloodstream in response to antigen (allergen) entry and leads to allergic reactions, we understand the necessity of determining the level of potential allergic background in HIV infection.

The study results revealed that the concentration of IgE in blood serum of individuals with this pathology was statistically significantly ($P<0.001$) 84.88 times higher than in healthy individuals – 54.32±3.20 IU/ml compared to 0.64±0.06 IU/ml, respectively.

The high allergic background observed in the studied individuals was attributed to the formation and development of opportunistic infections in their bodies, manifesting as protozoa (parasites) and fungal infections. This was explained as a consequence of secondary immunodeficiency developing in the organism due to the influence of HIV infection.

To provide a clearer picture of the differences in the obtained results, the indicators showing the degree of change in the concentrations of major immunoglobulin classes in the blood serum of HIV-infected individuals were presented in comparison to the parameters of healthy individuals (Table 2).

As evident, all the presented indicators have changed significantly ($P<0.001$). While the trend of changes in their values was practically uniform, a pronounced imbalance in the intensity of changes was observed, indicating alterations in the immune system of these individuals. It should be particularly noted that among the four immunoglobulins, the most significant changes were observed in the concentrations of IgG and IgE.

Table 2 – Ratio of serum immunoglobulin levels of individuals with primary HIV infection to indicators of healthy individuals, in times

Immunoglobulins	HIV-infected persons, n=90
IgA	1,95* ↑
IgM	1,51* ↑
IgG	2,46* ↑
IgE	84,88* ↑

Note: * – sign of reliable difference in relation to the indicators of healthy individuals; ↑ – directions of change.

It is also important to conduct a comparative study of cytokine concentrations, which are other representatives of humoral immunity, in the blood serum of individuals with primary HIV infection. Although these indicators were studied and described in detail by Zalyaliyeva M.V. and Ruzibakiyev R.M. [8], they were determined in relation to the stages of the disease, and individuals with primary HIV infection were included in the general group. For this reason, the necessity of studying them and evaluating their results arose.

It is known that for complete protection against HIV infection, the participation of CD4+ cells is required in addition to cytotoxic T-lymphocytes. This is because CD4+ cells synthesize cytokines and chemokines that inhibit HIV replication [8]. Two types of CD4+ cells are distinguished: T-helper type 1 (Th1) and T-helper type 2 (Th2), both of which are derived from their common precursor, Th0 [1, 5]. Th1 helpers produce cytokines that stimulate cellular immunity, while Th2 helpers ensure the production of cytokines that facilitate the transformation of B-lymphocytes into plasma cells.

As demonstrated, IL-1 is an inflammatory cytokine that acts as a mediator of immunity and inflammation. It is synthesized by macrophages, stimulated B-lymphocytes, T-lymphocytes, keratinocytes, and fibroblasts. In the primary immune response, its production triggers pathogenetic changes associated with the disease that caused its production [2-4]. Taking into account the aforementioned facts, it was deemed necessary to identify this cytokine in viral infections, including HIV infection.

The study revealed that the serum concentration of IL-1β in individuals with primary HIV infection reached 46.36±2.67 pg/ml, which shows a significant ($P<0.001$) 5.75-fold increase compared to the same parameter in healthy individuals (8.06±1.23 pg/ml) (Table 3).

Table 3 – Results of the study of humoral immunity parameters of individuals with primary HIV infection

Parameters	Healthy individuals, n=20	HIV-infected persons, n=90
IL-1β, pg/ml	8,06±1,23	46,36±2,67 * ↑
IL-6, pg/ml	6,80±1,06	10,20±0,76 * ↑
IL-4, pg/ml	5,85±0,99	36,33±1,88 * ↑
IL-10, pg/ml	17,31±3,00	33,49±2,13 * ↑

Note: * – sign of reliable difference in relation to healthy individuals; ↑ – direction of change.

Its increase leads to the formation and development of disease symptoms and HIV-induced Th1-cell deficiency. Consequently, an increase in IL-1β concentration is associated with Th1-cell deficiency, and this pathological state contributes to the development of inflammatory disease symptoms (fever, anemia, weight loss, and pathological changes in the skin and mucous membranes).

IL-6 is another cytokine characteristic of inflammation that plays a significant role in HIV infection. Considering that IL-6 is synthesized by activated macrophages and Th2 cells, stimulates the immune response, serves as one of the crucial mediators in the acute phase of inflammation, promotes the proliferation and differentiation of T and B cells, stimulates leukopoiesis, and activates lipid synthesis in the liver, we can be certain of its importance as a cytokine [6, 9].

The study found a statistically significant ($P<0.05$) increase of 1.50 times in the concentration of IL-6 in individuals with primary HIV infection compared to healthy individuals – 10.20±0.76 pg/ml versus 6.80±1.06 pg/ml, respectively (Fig. 1).

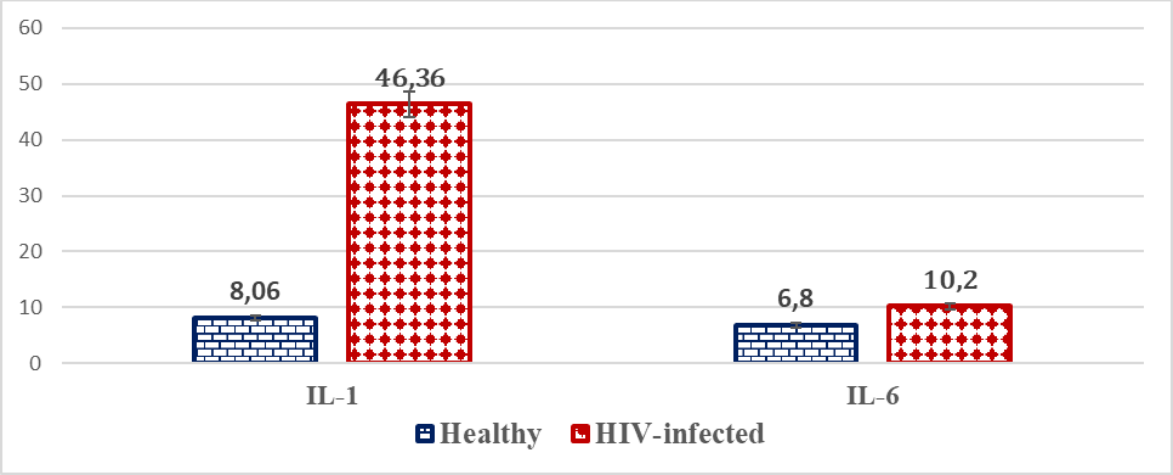

Figure 1 – Parameters of pro-inflammatory cytokines in the blood serum of individuals with primary HIV infection, pg/ml

The lower intensity increase of IL-6 in blood serum compared to IL-1β indicates the formation and development of the inflammatory process and its relatively minor role in antiviral immunity.

In the subsequent stage of the study, the concentrations of anti-inflammatory cytokines (IL-4, IL-10) in blood serum were comparatively analyzed.

Today, it has been demonstrated that IL-4 is an anti-inflammatory cytokine that induces the differentiation of Th0 cells, is synthesized by Th2 cells, eosinophils, basophils, and mast cells, enhances the proliferation of T and B lymphocytes, facilitates the differentiation of B lymphocytes into plasma cells, and serves as an important regulator of humoral and adaptive immunity [7].

It has been determined that the cytokine IL-4 inhibits the expression of HIV co-receptors on the surface of T-lymphocytes, thereby reducing the likelihood of viral entry into the cell. However, simultaneously, through tat-dependent mechanisms, it enhances HIV replication in the cells of the virus-infected organism [8]. Hyperproduction of IL-4, especially in the early stages of HIV infection, increases the ability of infected cells to form syncytia, which facilitates a more rapid progression of HIV infection.

In the conducted study, the concentration of IL-4 cytokine in blood serum was found to be 36.33±1.88 pg/ml in individuals with HIV infection, which was statistically significantly higher (6.21 times) than the indicators in healthy individuals (average 5.85±0.99 pg/ml) ($P<0.001$).

IL-10 is one of the anti-inflammatory cytokines that possesses numerous pleiotropic effects, including anti-inflammatory and immunoregulatory properties. It inhibits the induction of TNF-α and IL-1β cytokine secretion by Th1 cells, effectively suppressing the inflammatory process that has developed in the body [11].

The study revealed that the concentration of this cytokine in the blood serum of individuals with primary HIV infection significantly increased by 1.94 times compared to healthy individuals – 33.49±2.13 pg/ml versus 17.31±3.00 pg/ml respectively ($P<0.001$). Although the intensity of changes was lower compared to IL-4, the trend of changes remained the same. Consequently, a sharp increase in the concentration of anti-inflammatory cytokines was observed in HIV infection (Figure 2).

The results obtained from studying the concentrations of anti-inflammatory cytokines in the blood serum of individuals with primary HIV infection were similar to those reported by many researchers, including Zalyaliyeva M.V. and Ruzibakiyev R.M. [8]. In this context, a comparative analysis was conducted on the degree of changes in all studied pro-inflammatory and anti-inflammatory cytokines relative to healthy individuals (Table 4).

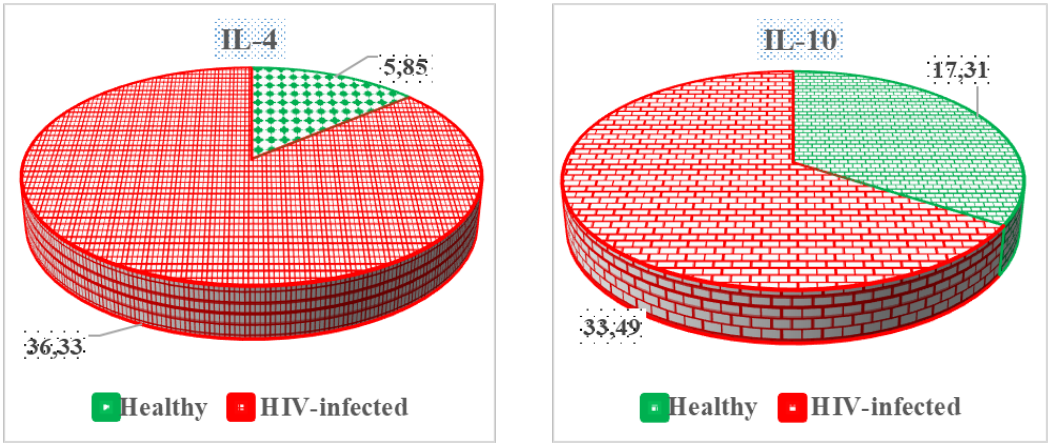

Figure 2 – Parameters of anti-inflammatory cytokines in the blood serum of individuals with primary HIV infection, pg/ml

Table 4 – The ratio of cytokine levels in the blood serum of individuals with a primary HIV infection to the parameters of healthy individuals, in times

Cytokines		HIV-infected persons, n=90
Pro-inflammatory	IL-1β	5,75 * ↑
	IL-6	1,50 * ↑
Anti-inflammatory	IL-4	6,21 * ↑
	IL-10	1,93 * ↑

Note: * – sign of reliable difference in relation to healthy individuals; ↑ – direction of change.

As evident, hyperproduction of all cytokines (both pro-inflammatory and anti-inflammatory) was detected and significantly altered compared to the indicators in healthy individuals. It is noteworthy that while the trend of changes is consistent, the intensity of these changes varies.

Individuals with primary HIV infection exhibited significant changes in immunoglobulin concentrations compared to healthy individuals, demonstrating a quantitative imbalance. Although the trend of changes was consistent among these individuals, the intensity of changes varied. A statistically significant increase was observed in the examined individuals compared to healthy subjects: IgA levels were 1.95 times higher, IgM levels were 1.51 times higher, and IgG levels were 2.46 times higher ($P<0.001$). This situation indicated a strain in the primary immune response alongside strengthened local and humoral immunity, while also revealing a clear deficiency in the secondary immune response.

A significant and sharp increase in IgE levels in the blood serum of HIV-infected individuals by 84.88 times ($P<0.001$) indicates the formation and intensification of an allergic background in the bodies of these individuals. In our opinion, this condition is associated with an increase in the number of protozoa (parasites) and microscopic fungi (opportunistic infections) due to the development of secondary immunodeficiency in the body. Consequently, the formation of secondary immunodeficiency in individuals with HIV infection was manifested by a quantitative imbalance of immunoglobulins in their blood serum.

The levels of pro-inflammatory cytokines (IL-1β, IL-6) in the blood serum of individuals with newly diagnosed HIV infection were found to be quantitatively increased in the studied pathology. Although the trend of increase was similar for both cytokines, the intensity of quantitative changes varied. Compared to healthy individuals, the increase in IL-1β was 5.75-fold, while for IL-6 it reached 1.50-fold. Evidently, the role of IL-1β in the development of the inflammatory process and antiviral immunity was more significant than that of IL-6.

It was noted that the concentrations of both cytokines in this group were significantly higher compared to healthy individuals, by 6.21 and 1.94 times respectively (P<0.001). The detection trend of both cytokines and the intensity of changes relative to healthy parameters were practically identical. It was acknowledged that both of the interpreted cytokines play a role in antiviral immunity, including immunity against HIV infection.

Conclusion

1. Although individuals with primary HIV infection showed similar trends in changes of serum immunoglobulin concentrations, the intensity of these changes varied. In the studied subjects, IgA levels increased by 1.95 times, IgM by 1.51 times, and IgG by 2.46 times compared to healthy individuals (P<0.001). This situation indicated the presence of strain in the primary immune response along with the strengthening of humoral immunity, but a pronounced deficiency in the secondary immune response.

2. A significant 84.88-fold increase in IgE levels in the blood serum of individuals with HIV infection indicates the formation and intensification of an allergic background in the bodies of these individuals. The development of this allergic background was considered to be associated with an increase in opportunistic infections due to the secondary immunodeficiency that has developed in the body.

3. The concentrations of IL-1β and IL-6 in the blood serum of individuals with primary HIV infection were quantitatively increased. Compared to the levels in healthy individuals, the increase was 5.75-fold for IL-1β and 1.50-fold for IL-6. The role of IL-1β in the formation of the inflammatory process and antiviral immunity was more significant than that of IL-6.

4. The levels of IL-4 and IL-10 in the blood serum of individuals with primary HIV infection were found to be significantly higher than in healthy individuals, by 6.21 and 1.94 times respectively. The detection trend of both cytokines and the intensity of changes relative to the parameters of healthy individuals were practically identical.

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