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" Inflammatory diseases of the genitals in HIV-infected women" (monograph)

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In this monograph, the clinical and immunological characteristics of inflammatory diseases of the genital organs in HIV-infected women are studied for the first time and assessment methods are created. The monograph reveals that human papillomavirus type 16 is recognized as an oncogenic risk factor in diseases of the external genital organs, in addition, the relationship between activation markers and the representativeness of lymphocyte subpopulations is studied depending on the presence and absence of antiretroviral therapy. Changes in the immune system in HIV-infected women with inflammatory diseases are revealed, which, in turn, allows us to identify differentiated tactics for assessing the immune status of women.

The monograph is intended for general practitioners, gynecologists , immunologists, masters, clinical residents and students of medical institutes.

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LIST OF ABBREVIATIONS

AG	-	Antigen
AZETS	-	Antibody-dependent cellular cytotoxicity
APK	-	Antigen presenting cell
ART	-	Antiretroviral therapy
ASL	-	Antigen binding cells
AT	-	Antibodies
BGL	-	Large granular lymphocytes
BTSh	-	Heat shock proteins
IVIG	-	Intravenous immunoglobulin
VZG	-	Inflammatory diseases of the genitals
VIN	-	Secondary immune deficiency
HIV	-	Human immunodeficiency virus
HRT	-	Delayed-type hypersensitivity
GFR	-	Hepatocyte growth factor
EK, NK	-	Natural, organic cytotoxicity
IZSD	-	Insulin-dependent diabetes mellitus
IL	-	Interleukin
IPFR	-	Insulin-like growth factor
IS	-	Stimulation index
IFA	-	Enzyme immunoassay
IFN	-	Interferon
IEL	-	Intraepithelial lymphocytes
Kon A	-	Concanavalin A
KSF	-	Colony stimulating factor
LG	-	Luteinizing hormone
LPS	-	Lipopolysaccharides
MNC	-	Mononuclear cell
MP	-	Metalloproteinases

NE	-	Unconjugated estriol
PD	-	Prenatal diagnosis
PCR	-	Polymerase chain reaction
PEG	-	Polyethylene glycol
PYAL	-	Polymorphonuclear leukocytes
RTML	-	Lymphocyte migration inhibition reaction
SMF	-	Mononuclear phagocyte system
SLEEP	-	Acquired immunodeficiency syndrome
TBG	-	Trophoblastic β glycoprotein
TFR	-	Transforming growth factor
FAN	-	Phagocytic activity of neutrophils
FAT	-	Platelet activating factor
FGA	-	Phytohemagglutinin
FRB	-	Early pregnancy factor
HA	-	Chromosomal aberrations
hCG	-	Human chorionic gonadotropin
Central Election Commission	-	Circulating immune complexes
CD	-	Differentiation cluster
HLA	-	Human leukocyte antigen
Ig	-	Immunoglobulin
LFA	-	Lymphocyte functional antigen
PAPP , A	-	Pregnancy-related plasma protein
TCR	-	T cell receptor
Th 1	-	T helper type 1
Th 2	-	T helper type 2
TNF	-	Factor necrosis tumors ne with rose factor)

GUIDANCE

A number of scientific studies are being conducted worldwide to achieve high efficiency of measures aimed at treating and preventing gynecological diseases in women living with HIV. In this regard, it is necessary to identify the main features of the development of diseases of the genital organs against the background of HIV infection and to substantiate the causes of the negative changes that arise.

It is important to reduce the risk of developing resistance to antiretroviral drugs, improve approaches to the treatment and prevention of opportunistic infections, concomitant syndromes, identify changes in the immune system, increase the effectiveness of preventive measures to improve the quality of life of women, reduce complications and treat them. In this situation, the main task is to restore the functional reproductive system of women with the subsequent birth of children without congenital HIV infection, as well as to protect the partner from the transmission of this infection. Such goals are achievable by following the rules for the treatment of HIV-infected women with the appropriate therapy, as well as controlled conception of a child with further observation of the entire period of pregnancy.

Today, large-scale work is being carried out among various segments of the population, aimed at early diagnosis and reduction of complications of somatic diseases, especially among women, creation of a healthy environment, and the spread and prevention of HIV/AIDS. The Strategy of Actions for Five Priority Areas of Development of the Republic of Uzbekistan for 2017-2021 defines the following tasks: “...increasing the availability and quality of specialized medical care, further reforming emergency and urgent medical care, preventing disability...” defined. In this regard, it is important to raise the level of medical services to a new level, to develop tactics for early diagnosis and treatment of gynecological diseases in HIV-infected women, especially to reduce the number of complications.

This dissertation research to a certain extent serves to fulfill the tasks provided for in the Resolution of the President of the Republic of Uzbekistan dated 01/25/2018 No. PP-3493 “ On measures to further improve the system of counteracting the

spread of the disease caused by the human immunodeficiency virus in the Republic of Uzbekistan ”, Resolutions of the President of the Republic of Uzbekistan No. PP-4887 of November 10, 2020 " On additional measures to ensure healthy nutrition of the population " and No. PP-4891 of November 12, 2020 "On additional measures to ensure public health by further improving the effectiveness of medical prevention work" as well as in other regulatory documents related to activities in this area.

This dissertation research was carried out in accordance with the priority direction of development of science and technology of the Republic of Uzbekistan VI "Medicine and Pharmacology".

At present, there is a large number of articles examining various indicators of the spread of HIV. In a general sense, they are classified into articles in a global context, considering all countries of the world, and articles focusing on countries that are hotbeds of the disease. An analysis of the influence of social and economic determinants on the global spread of HIV and AIDS has been conducted (Broz., D . et al ., 2014; Cock ., K . M. et al ., 2012).

The analysis included 151 countries and took into account 90 explanatory variables. In total, five key aspects were analyzed: the number of people infected with HIV/AIDS per 100,000 population; the number and percentage of adults aged 15–49 years living with HIV-infected status; the estimated number of deaths from AIDS; the percentage of patients diagnosed with HIV acquired sexually. The study by Moskaleva E. V., et al., (2017) emphasizes the importance of studying the socio-economic factors in the spread of socially significant diseases. It is noted that the majority of those infected are women, for example, in South Africa, women with AIDS make up 60% of all infected adults and 75% of infected adolescents. (Auvert B ., et al . 2015).

In modern conditions, the clinical course of inflammation has changed: the frequency of latent forms of the disease with periods of exacerbation has increased, which undoubtedly creates significant difficulties in diagnosing the inflammatory process and contributes to the insufficiently high effectiveness of routine treatment methods. (Kolpakova O.I., et al., 2016).

There are no studies in the literature devoted to the assessment of immunosuppression markers in inflammatory diseases of the genitals in HIV-infected women (Mukharyamova L.M., et al., 2017). In the Republic of Uzbekistan, the problem of inflammatory diseases of the genitals in women with HIV infection is insufficiently covered. There are isolated reports concerning some issues of diagnosis and treatment (Zalyalieva M.V., et al., 2010). Particular attention is paid to the prevention of the spread of the disease in hospitals, especially in the obstetric profile. At the state level, an assessment is made of the degree of coverage of patients with antiviral therapy and its pharmacoeconomic effect (Atabekov N.S., et al., 2017). However, AIDS is still one of the leading causes of death worldwide.

CHAPTER I. THE CURRENT STATE OF THE AIDS-HIV PROBLEM IN WOMEN OF REPRODUCTIVE AGE WITH INFLAMMATORY DISEASES OF THE GENITALIA

Socio-behavioral factors (early onset of sexual activity, changing moral standards, promiscuity, prostitution, non-traditional forms of sex, low standard of living, uncontrolled use of antibiotics and spermicides, abuse of sweets) [8, 9, 10].

A key role in the generalization of the infectious process with its subsequent spread to the uterine appendages and upper genital tract is played by a violation of the immune defense mechanisms of the macroorganism [4].

PIDs begin with infection of the vagina, cervical canal, urethra with pathogens such as Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonada vaginalis, mycoplasma or their associations. The balance between lactobacilli and pathogenic microflora in the vagina is disturbed, with the latter predominating. Violation of the biocenosis of the vagina and cervical canal creates conditions for unimpeded penetration of infection into the upper parts of the genital tract (endometrium, fallopian tubes, ovaries, urethra, bladder, and in some cases, into the parietal peritoneum) [4]. Most pathogens of STIs are weak antigens, which causes a latent course of infection (the so-called "silent salpingitis"). This, in turn, leads to late diagnosis and irrational antibiotic therapy.

Inflammatory diseases of the genitals are common in 50-60% of women worldwide and remain one of the most pressing problems of the gynecological specialty. In many cases, inflammatory diseases of the genitals appear in the fertile age, leading to disruption of not only the reproductive function, but also the functioning of other body systems. According to the World Health Organization, " ... HIV infection is registered among women aged 25-34 years, and 1.2% of women in this age group are considered infected with this infection ... ". The spread of HIV infection is currently growing exponentially, even taking into account all measures aimed at preventing its spread. There are currently more than 36.7 million HIV-infected people. The HIV/AIDS epidemic threatens the sustainable development of

society in many countries of the world. The growth of the epidemic leads to the deepening of social problems, which in turn can threaten economic development.

Sexually transmitted infections (STIs) are among the best known risk factors for human immunodeficiency virus (HIV) infection, facilitating HIV transmission by disrupting protective mucosal barriers and recruiting susceptible immune cells (CD4+ T-helper cells, macrophages) to the site of infection [1]. Non-ulcerative and ulcerative STIs also provide a gateway for HIV to access susceptible cells. With a single unprotected sexual contact, genital ulcers increase the risk of HIV transmission by 50–300 times [2]. STIs can cause bleeding, for example, trichomoniasis and bacterial vaginosis increase the risk of vaginal bleeding by more than 12 times [3], which increases the risk of HIV infection during sexual activity [4]. Studies [5] have shown that syphilis in HIV-infected individuals is more often observed as a mixed infection: in 68% of cases it is associated with two or more STI pathogens. Because infection with STIs increases the risk of acquiring and transmitting HIV, successful treatment of these infections can help reduce the spread of HIV among people at high risk.

A MODERN VIEW OF THE ETIOPATHOGENESIS OF HIV INFECTION IN WOMEN OF REPRODUCTIVE AGE WITH INFLAMMATORY DISEASES OF THE GENITAL TRACT

HIV infection is an infection that significantly reduces a person's protective properties, caused by a virus that develops slowly over many years. HIV directly damages the human protective system, as a result of which the body becomes defenseless against external pathogens and the development of oncological diseases, the result of which is death [64; p. 905-908].

Referring to the historical data of the discovery of HIV infection, it is known that in 1981 in the USA an article was published which described 5 cases of Pneumocystis pneumonia and 30 cases of Kaposi's sarcoma in previously healthy representatives of non-traditional [145; pp. 45-54] . Thus, in 1982 the diagnosis was first formulated, which was called AIDS, but the reason for its origin was unknown [146; pp. 350-357] . In 1983, HIV was isolated from the cell culture of an infected person. The results of the first studies of the origin of HIV revealed that the highest concentration of HIV is concentrated in the countries of Central Africa [150; pp. 47-56] .

The etiological origin of HIV is due to an RNA-containing retrovirus, the genome of which consists of 3 structural genes: gag, env and pol. Gag regulates the synthesis of internal peptides; Env regulates the glycoproteins of the membrane envelope; Pol regulates the mechanisms of enzymes, and in addition, plays a role in the reverse transcription of the genome. HIV is classified into 2 types: HIV-1 and HIV-2. The human immunodeficiency virus is not viable in the external environment for a long period of time.

It dies at high temperatures (560 C), moreover, it is destroyed by disinfectants [163; pp. 335-353] . This virus differs from others in its resistance to ionizing radiation, ultraviolet radiation and low temperatures (-590-610 C). Although, it is noted that the pathogen, being in the external environment, can remain viable for several days in blood or sperm, even in dried form [152; pp. 122-129] .

The main source of infection is an infected person. In addition to blood, the virus is also found in the semen of infected people, menstrual blood and cervical secretions of infected women. There have also been cases of HIV infection in breast milk, lacrimal and cerebrospinal fluid, saliva, sweat, urine, biopsies, bronchial fluid and feces [10; pp. 15-18]. The routes of HIV transmission include sexual, blood contact and vertical. The main risk factor is concomitant inflammatory processes in the genital tract, which contribute to the opening of the gates for the pathogen. Blood infection occurs during blood transfusions from HIV-infected people, the use of medical instruments after an infected patient. Infection of health care workers has been detected in a ratio of 1/300 cases of contact with biopsies of HIV-infected patients. The vertical mechanism of transmission is due to the transfer of the pathogen from a pregnant mother to the fetus. In addition, infection of a child from a mother with HIV infection occurs through trauma to the birth canal and the child during natural childbirth, as well as during breastfeeding [10; pp. 15-18].

To penetrate the cell, the virus binds to the cell membrane receptor via the glycoprotein gp120. Indirectly through the plasma membrane, gp41 penetrates and fuses with it, thanks to the glycoprotein. As a result of the introduction of the HIV genome into the cytoplasm, via the enzyme reverse transcriptase, the viral RNA is rewritten on the cell DNA [5; pp. 26-33] . The result of this process is that the viral DNA becomes a model for the production of similar information. At the final stage, the virus particle assembles and leaves the cell. The entire life cycle of HIV is 1-2 days. As a result, billions of viral cells are produced during the day. The cell in which replication took place is eventually destroyed [14; pp. 93-99] .

HIV infection is characterized by a slowly progressive course. A patient who has neglected antiviral therapy lives on average 10-12 years. [16; pp. 46-47, 75; pp. 65-82].

Today, there is a certain classification of stages of disease development according to Pokrovsky [88; pp. 187-197, 89; pp. 47-54]:

1. Incubation stage

2. Stage of primary manifestations

A - asymptomatic seroconversion

B - acute infection without secondary diseases

B - acute infection with secondary diseases

3. Latent stage

4. Stage of secondary diseases:

A - body weight loss less than 10%;

B - progressive loss of body weight of more than 10%;

B - cachexia;

5. Terminal stage.

In laboratory diagnostics, it is possible to detect immunity to HIV infection, antigens and the genome of the virus. Currently, in addition to blood serum and the blood itself, there is a wide choice of biological material for detecting antibodies to HIV. The main and reliable analysis for determining antibodies is ELISA (enzyme-linked immunosorbent assay). If the ELISA gives a positive result, it is carried out several more times [85; p. 156] . If the results of subsequent tests give a positive answer, the IB (immune blotting) method is used, which is used to detect antibodies to specific HIV proteins. IB results can be **positive,** in which the presence of antibodies to two or three glycoproteins of the pathogen is observed for HIV-1 and HIV-2, or **negative,** in which the absence of antibodies to a particular antigen and **questionable are observed.** In this case, the presence of antibodies to one glycoprotein or any other for HIV2. Only after the conclusion of a positive IB result, a diagnosis of HIV infection of a person is possible [81; pp. 126-127, 96; pp. 119-127] .

On average, young women become infected with HIV 5-7 years earlier than young men [96; pp. 119-127] .

By November 1, 2020, 43,581 patients with human immunodeficiency virus were registered in the Republic of Uzbekistan. The incidence rate varies greatly depending on the region. High rates of this disease were recorded in Tashkent city, Tashkent, Andijan, Fergana and Samarkand regions. During the study period, 2,859,577 people were tested for HIV infection, of which 4,237 cases of infection

were identified. The gender division in 2014 was 44.6% for females and 55.4% for males. The main age group, which is 66.1%, was within 25-50 years. According to the routes of transmission, the leading role is occupied by sexual and amounts to 64.7%, while parenteral 24.4%. Among them, IDU makes up 6.9%, and the vertical route of transmission is only 0.2% [47; [p.3-6]. According to the results of the 2013 epidemiological surveillance study, the incidence of the immunodeficiency virus among people with an increased risk of infection was higher than 5%. In this group, the incidence among IDUs was 7.2%. These results lead to the conclusion that the epidemic stage is concentrated.

The majority of women infected with HIV are aged 24-35 years, 1.5% of women in this age group live with an established diagnosis of HIV. The main route of transmission of the human immunodeficiency virus is sexual intercourse. Infection during sexual intercourse occurs through the introduction of HIV-1 into immune cells, namely CD4, T cells, devourer cells, dendrocytes, Langerhans cells. HIV-1 provokes an inflammatory process after introduction into the CD4 cell. [19; p. 85-86]. A characteristic feature is the diversity of oncogenic viruses, an increased incidence of intraepithelial neoplasia of the cervical part, the process of formation of progressive malignant forms of cervical cancer. HIV infection is a predisposing factor for cervical cancer in the earlier period, the development of genital warts, due to damage to the external genitalia by HPV [20; p. 87]. In this category of patients, grade 2-3 cervical dysplasia is more common, as a result of damage to the epithelium. [22; p. 104].

A parallel was also found between the CD4 + cell level and the frequency of cervical epithelial damage [65; p. 905-908]. Before the introduction of ART, the frequency of uterine epithelial damage was 20% of patients who had been diagnosed with HIV more than 3 years ago. In 21-23% of HIV-infected patients with CD4 + cell levels below 200 cells/μl who are not sexually active, at least one type of human papillomavirus was detected [57; p. 23].

Some studies have shown that in the presence of HPV types 16 and 18 in patients who are also diagnosed with HIV, destruction of the uterus with the risk of

developing cervical cancer is more often accompanied, in contrast to women with a normal cytological smear. [76; p. 56].

There are also other data confirming that HPV-16 type is more common in HIV-infected patients, but in patients with a high degree of squamous intraepithelial lesion (HISL - high grade squamous intraepithelial lesions) no more than in the entire study group. In addition, HPV-52 type is more often determined in women with a positive HIV status, while HPV-45, on the contrary, is less often determined, in contrast to women with a negative HIV status. [77; p. 496].

Studies conducted to date show that women with a positive HIV status have a higher risk of developing persistent functional ovarian cysts, which in most cases leads to ovarian apoplexy [124; 245-255c]. The cause of the development of these processes in HIV-infected patients is coagulopathy, in particular thrombocytopenia. This is one of the reasons for emergency hospitalization and decreased fertility [128; 397-406 pp.].

When analyzing the genitourinary status of individuals with inflammatory diseases of the pelvic organs, human immunodeficiency virus [1; p. 121-124]. Diagnosis of chronic endometritis and severe diseases of the uterine appendages (purulent diseases of the fallopian tubes) are observed more often in people with human immunodeficiency virus. Loss of pregnancy in women is associated with STDs [2; p. 100-101].

Diseases of the female reproductive system have many factors. The first factor is the introduction of microbes from outside, the second is the exacerbation of opportunistic microflora during HIV, the third factor is the flora transmitted sexually - mycoplasma, chlamydia, ureaplasma, gonorrhea, but most often in combined variants [21; p. 41-46].

When conducting bacterial cultures, staphylococci and E. coli are most often isolated [27; pp. 4-9]. Against the background of inhibition of the immune response in HIV-positive individuals, an increase in the incidence of diseases such as herpes virus-2 and HPV is determined. In turn, the herpes virus type 2 has the property of

increasing the viral load, which in turn increases the clinical picture of HIV infection and the ability to infect [127; pp. 107-116].

Sexually transmitted infections provoke the growth of the virus in sperm and vaginal secretions, and also increase the secretion of target cells (CD4 +) for HIV infection. In the presence of STIs, the ability to transmit the virus increases due to damage to the mucous membranes, skin, etc. [130; p . 346-350]. Latent cervicitis most often develops against the background of the human immunodeficiency virus. In 2/3 of females who sought hospital treatment with complaints of ulcers, herpes rash or HPV, HIV infection was diagnosed [23; p. 81]. In HIV-positive workers in China in the field of intimate services, chlamydia was diagnosed in 60%, trichomoniasis was detected in 43% of cases, and goroneya was detected in 38%. Treatment of these diseases helps to reduce the likelihood of infecting a partner [134; pp . 2183–2191]. Condyloma and trichomonas are most often found in individuals infected vertically during pregnancy [136; pp . 329–340].

Also, carriers of the human immunodeficiency virus have an increased chance of diagnosing bacterial vaginosis caused by mycoplasma and gardnerella. It should be taken into account that the damage to the reproductive system has multiple etiologies. The first factor is the introduction of microbes from outside, the second is the exacerbation of opportunistic microflora during HIV, the third factor is sexually transmitted flora - mycoplasma, chlamydia, ureaplasma, gonorrhea, but most often in combination, and due to a decrease in the immune response and the amount of CD 4 + , they create conditions for the occurrence of sexually transmitted infections that provoke the growth of the virus in sperm and vaginal secretions, and also increase the secretion of target cells (CD4 +) for HIV infection. In the presence of STIs, the ability to transmit the virus increases due to damage to the mucous membranes, skin, etc. [146; p . 350-357]. Diagnosis of vulvar intraepithelial neoplasia and vulvovaginitis caused by various reasons is diagnosed much more often in individuals with the presence of the human immunodeficiency virus [17; p. 117-121]. VG-2 in HIV-positive patients can be manifested as false epitheliomatous hyperplasia, which at the cellular level is similar to flat cancer, genital warts (condylomas) are based on

low-concentration 6 and 11 HPV variants, and their occurrence with the level of immunosuppression. Also, HIV-infected people have an increased risk of developing Candida fungus albicansy , which disappears as immunity grows. Fungal infections occur due to early HIV infection or due to taking antibiotics [30; pp. 82-89].

Numerous studies have proven the high susceptibility of endometrial cells to cytomegalovirus, the long-term accumulation of which leads to chronic inflammation of the uterine mucosa in individuals with low immunity [37; p. 25]. L. Clark, in the process of studying the secretion of the uterine mucosa in 147 women with manifestations of inflammatory diseases of the pelvic organs, found an antigen to cytomegaloviruses in 21% of patients [40; pp. 81-86]. Herpetic lesions of the uterine mucosa occur in individuals with non-classical or asymptomatic forms of herpes, due to the long presence of the virus on the mucous membranes. In 1989, M. Peuchaur first recorded the presence of inflammation of the uterine mucosa against the background of the human immunodeficiency virus, during which the division of HIV in the cells of the monocyte-macrophage group of the uterine mucosa was confirmed due to the introduction of in situ and immunohistochemical analysis.

THE ROLE OF IMMUNOLOGICAL FACTORS IN THE PATHOGENESIS OF HIV INFECTION IN WOMEN OF REPRODUCTIVE AGE WITH INFLAMMATORY DISEASES OF THE GENITALIA

Nowadays, there are a significant number of factors that determine the dynamics of virus progression and the outcome of the disease. The main factor in the penetration of the virus into cells is cellular tropism, which is mediated by the determination of the viral phenotype and receptor interactions. But the mechanism of development of factors that contribute to the fact that the number of CD 4^+ T cells decreases and, at the same time, the number of X4- R 5-tropic strains increases in AIDS, has not yet been fully studied. The nature of the course of the disease and the time of its manifestation depend on the specificity of the immune response, this is due to the activity of T cells and the level of organization of the immune system. Thus, these indicators are carefully studied and taken into account. In addition, special

attention is paid to the study of cytokines. Cytokines play an important role in the activation of the immune response. In the course of the study, it was found that the spread of HIV infection throughout the body affects the formation of cytokines by changing the activity of T cells. This is the reason for the decrease in immunity, creating favorable conditions for the reproduction of HIV [42; p. [223-225] .

Cytokines are divided into Th 1 and Th 2. Th 1 type is responsible for cellular immunity and is pro-inflammatory, and Th 2 type is responsible for humoral immunity and is anti-inflammatory. Thus, as HIV infection progresses, the level of TNF-γ increases, which promotes increased cytokine activity. $CD8^{+}$-T cells, in turn, lead to the death of infected cells.

It is noteworthy that the production of Th 1 cytokines in HIV-infected individuals is sharply reduced, in contrast to Th 2, the level of which is increased. Type 2 cytokines also include IL -10, which is an immunosuppressant and acts in tandem with IL -4. Together, they limit the action of Th 1 cells [45; pp. 9-14] .

Penetration of HIV into human T-cells is facilitated by CD4 + molecules and chemokines. In order for the virus to replicate, reverse transcriptase enters the process, copying HIV RNA. This process is accompanied by various mutations, which leads to new genotypes of the virus, reducing the body's immune response. Under the influence of integrase, the DNA of the infection combines with the DNA of the infected. During mitosis, the viral DNA divides in the same way as the DNA of the infected [54; p. 81-84, 102, p. 185] . As a result, the viral DNA is translated into RNA to HIV proteins, which together form virions inside the cell membrane, and then bud off from it into its cell membrane. Then, the process of transforming the immature virion into a mature one occurs, using the protease enzyme. Affected lymphocytes produce more than 90% of virions. In case of suspension of antiviral treatment, the reserve of HIV-infected $CD4^{+}$ $^{\text{lymphocytes}}$ is used.

In blood plasma, the half-life of virions lasts for 5 hours. In severe stages of HIV, over 100 virions are produced and excreted daily. HIV resistance to antiviral drugs is due to the large volume of viral replication and mutation, which increases the production of new strains that are resistant to human immunity. [154; p. 19035] . In

contrast to healthy uninfected individuals, the period of elimination of CD 4+ lymphocytes in HIV-infected individuals is 2 days, which is several times slower. In most cases, the initial stage of infection is the highest in terms of HIV levels in blood plasma, thus reducing the number of ^{CD} 4+ lymphocytes . If the number of lymphocytes drops to less than 199 μl, then opportunistic microorganisms become activated.

In addition, humoral immunity is affected and active proliferation of B cells occurs in the lymph nodes, leading to lymphadenopathy.

The diversity of HIV-1 is due to reverse transcriptase. Along with this, there are other factors that affect the modification of various forms of the virus. These include cytopathic ability (CPE), resistance to immune defense, tropism. Depending on the cellular tropism, HIV-1 strains are divided into three groups, which include macrophage-tropic (M-tropic), non-syncytium-inducing phenotype (NSI), T-tropic, with a syncytium-inducing phenotype (SI) [151; p. 1417-1425]. In addition to them, there are strains with dual tropism. M-tropic HIV-1 infect monocytes, macrophages and T-lymphocytes in the blood. T-tropic infect isolated T-lymphocytes and T-cell lines. Strains with dual tropism can affect both. The presence of SI strains is detected by a decrease in the number of T-lymphocytes, as well as by the rapid progression of HIV along with NSI strains . At the moment, all the nuances remain unstudied, for example, whether one strain transforms into another or they arise autonomously is unknown. It is noteworthy that in 55% of cases of fatal AIDS among infected individuals, the SI strain prevails [67; p. 106-108] .

A significant role in the subsequent study of all the intricacies of HIV, especially cellular tropism, was played by the discovery of coreceptors, which are the entry gates for the penetration of the virus necessary for the penetration of HIV. The most basic chemokine receptors are CCR5 and CXCR4. According to prevalence among various cells, the CCR5 receptor is noted. They are most susceptible to damage by HIV infection, along with monocytes, macrophages and T-cells. In turn, the penetration of M-tropic strains into monocytes, macrophages and T-lymphocytes is carried out through the CCR5 coreceptor. T-tropic strains, forming T-cell lines and

T-lymphocytes, use the CXCR4 coreceptor as the main one. HIV strains with dual tropism use both types of coreceptors [79; p.36-41] .

Data based on experiments conducted in laboratory conditions on experimental animals are reliable and prove that during sexual contact with an infected person, HIV infects a small volume of CD4+ T-lymphocytes, macrophages and dendritic cells, which are localized directly on the lamina propria. It is said that the introduction of the virus is carried out by means of an endotranscitor, contact with class C lectin receptors located in dendritic cells and macrophages. Initial cell division occurs in local lymph nodes, which leads to the initial activation of the virus [157; p. 204-210] . The movement of infected T-lymphocytes into the general bloodstream leads to secondary activation of the virus in the gastrointestinal tract, bone marrow and spleen with their subsequent infection.

At the apogee of migration (from 105-110 viruses in ml of plasma) the clinical first stage of HIV infection begins to develop. The values of chronic migration are 1-2 orders of magnitude lower than the apogee values. This occurs due to the response of CD8+ cells, as well as a decrease in the target cells of the virus. When entering the body, the virus is homogeneous, but in the process of migration and introduction into the cells of organs, the virus mutates with subsequent development of resistance to therapy and further transition to a chronic state in the cells "reservoirs". In the early stages of infection, patients experience a strong decrease in the function of CD4+ T-cells, which are localized in the lymphatic areas of the mucous membrane, and this remains for a long period after the start of therapy [110; p. 35] .

It is worth noting the possibility of normalizing the number of CD4+ T cells during treatment. A decrease in the number of CD4+ T cells occurs under the influence of HIV infection by reducing the formation and lifespan of these cells. The virus destroys CD4+ cells, but their destruction also occurs due to the activation of the immune response and cell aging. In the early stages of infection, a decrease in the concentration of CD4+ T cells is noted, followed by their recovery to optimal values and their subsequent slow reduction down to 50-100 units per μl. The strongest effect is caused by the global inoperability of CD4+ cells in the gastrointestinal tract. In

addition to a decrease in the global number of CD4+ cells, changes in the composition of T cells are also noted, in particular, the mass death of T-helpers-17 and MAIT lymphocytes (mucosal associated invariant T - cells), which play an important role in the protective response to bacterial infection. Inhibition of T-cells in the gastrointestinal tract leads to an increase in flora products (lipopolysaccharides) in the blood plasma. And of course, the death of reticular fibroblasts and the accumulation of collagens, together with a decrease in the development and maintenance of IL -7, leads to inhibition of CD4+ and CD8+ T-cells [22; p. 104].

The clinical picture of HIV infection is based on the stimulation of both innate and acquired responses with impaired coagulation processes. The virus affects Troll - like receptors (TLR 7 and TRL8), activated on the surface of dendritic cell membranes, promoting the formation of INF α and TRL 4, both of which are involved in the formation of proinflammatory cytokines IL -6 and tumor death factors-α (TNF α) [79; pp. 36-41] . Also important is the reduction in the ratio of T-helpers17 to T-cells of the gastrointestinal tract and the progression of co-infection with viruses (cytamegalovirus causing an increase in T-cells) [113; pp. 78-97] . The inflammatory process in HIV persists even after stabilization of the level of CD4+ T-cells against the background of ART therapy. Many scientific works confirm high mortality of cardiovascular, liver and nervous system diseases in HIV during ART due to residual inflammation. For many years, due attention was not paid to the spread of HIV in the body by means of contacts between cells, which turned out to be thousands of times more effective than classical spread [124; p. 593-600]. This mechanism was organized due to the antipathy of protective synapses. Spread of infection begins after the appearance of an infected synapse, which is accelerated by the available adhesive molecules. Thus, an infected CD4+ T-cell secretes the HIV rim protein ^p120^p41 on the outer membrane. The conditions for the formation of such passages are the presence of CD4+ receptors on the surface of the cell membrane accepting the contact, the absence of coreceptors (CCR 5 or CXCR 4) does not affect the transmission in any way, but leads to the impossibility of division of the infection. The cell carries out transmission in two ways, which can work

simultaneously. The first method is based on the budding of the virus with the release of infection into space and subsequent capture of varions by the recipient cell [111; p. 1545-1550] . The second method consists of the formation of membrane growths (nanotubes or phalopodium) to the neighboring cell, forming a “bridge”. Due to the chronicization of the inflammatory process during HIV infection, the blood composition is characterized by an abundant number of T- and B-lymphocytes, killers and helpers, and anti-inflammatory cytokines together with chemokines. The protein that is part of the gp 120 membrane, being in the free blood flow, induces, upon contact with such cytokines and interferons as IFN α and INFy IL 6, IL 10, IL 1 α and IL 1beta, TNF –α, but at the same time has no effect on IL -2,4,6 and TNF - α. Increased concentration of inflammatory precursor cytokines leads to sepsis, brain growths, cachexia and autoimmune processes [2; p. 100-101].

Massive damage to monocytes and macrophages does not depend on the state of CD4+ T cells, but plays a major role in the activation of opportunistic microflora. During HIV, macrophages undergo changes and reduce the production of active oxygen and chemotaxis decreases, and dysfunction of Fc and C 3 receptors, responsible for antimicrobial activity, is also observed. [100; p. 9-10, 135; p. 111-175].

By affecting B-lymphocytes, HIV increases the synthesis of IgG . This process increases with the development of the infection and its amount is 5%. The most antigenic proteins to viruses are gp 120, gp 21 of the viral envelope and nucleoplastid proteins p 24,17. [105; p.197, 139; p.109-117].

TREATMENT TACTICS FOR FEMALES WITH HUMAN IMMUNODEFICIENCY VIRUS WITH INFLAMMATORY GENITAL DISEASES

Since 1982 and up to the present day the immunodeficiency virus has been detected all over the world. The methods of treatment have been significantly simplified due to the experience and knowledge of the clinic. Based on modern medicine, patients with this infection are no longer considered incurable and

currently HIV is a chronic, long-term and controllable disease. This achievement has become possible due to the conducted research of HIV infection, and most importantly, the development and introduction into clinical practice of antiretroviral therapy (ART) [55; pp. 24-33, 92; pp. 4-12]. After the discovery and introduction of ART, the unthinkable happened: within a couple of years the disease changed its status from fatal to chronic, controllable by means of therapy. Nowadays, HIV-infected people are no different from healthy people, they live, work and are socially adaptive in the same way [58; pp. 94-96, 94; pp. 361-368].

Since we do not have the ability to completely eradicate the virus from the body, treatment is reduced to improving the quality of life and prolonging its duration. Treatment is based on eliminating the development of various concomitant pathologies, in particular, the activation of opportunistic flora. Therefore, basic etiotropic therapy of patients with HIV infection will include antiviral therapy and prevention of concomitant diseases. The main criterion for ART therapy is the presence of clinical disease [60; p.89-90, 90; p.83-88].

The mental health of this group is protected, since the disease is a severe stress [61; p.395-397]. The consequences of the human immunodeficiency virus are not encouraging. But with timely administration of ART therapy, there is a chance of a favorable outcome. This therapy ensures the limitation of progress and its retention in a chronic, weakly ongoing form. Due to the introduction of HAART, the level of fatal outcomes in people with CD4+ lymphocytes below 100 was reduced by 3 times [63; p.147-151].

Indicators for starting ART therapy are AIDS-related diseases, CD4+ lymphocyte count below 350, and hepatitis B. Some scientists recommend starting this therapy when there are 350-500 cells/mm3 ^{CD4} + lymphocytes (Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, 2010) [66; p. 102-103]. ART therapy is prescribed for life, and even during childbirth, zidovudine is continuously infused intravenously with other antiretroviral drugs. Providing care to patients with HIV infection is one of the leading problems. According to UN data for 2015, over 37 million people were

registered on the planet, 48.5% (18 million) of whom were women. The incidence rate is increasing among women. Due to the use of HAART, HIV infection has become a chronic infection with drug control. This has led to the formation of HIV-infected groups [39; p. 75-80].

Due to the suppression of immunity, secondary diseases develop. Also, due to the increase in the average age of patients with HIV infection, there was an increased number of visits to doctors with complaints of pathologies due to age. In addition to life expectancy, there was an increase in the quality of life of people with immunodeficiency. A feature of the course of this disease in the modern world was the detection of this pathology in women in socially favorable conditions. Among women in the reproductive period, the incidence rate was 45% in 2014. Due to this growth, the registration of pregnancies with HIV infection with the subsequent birth of sick children was increased [64; p.158-160].

To date, several features of the course of HIV in women have been identified [80; p. 135-150]. These features include: vertical and horizontal transmission of infection, side effects of HAART therapy, increased risk of infection during sexual contact, relatively high mortality, incidence of mental manifestations such as depression, etc. It has been established that the clinical picture develops more strongly with a lower level of infection with the virus compared to men. These facts require a special approach to the treatment of HIV infection in women. [82; p. 293].

It has been established that prophylactic treatment of STIs does not reduce the risk of HIV infection, especially classical treatment with acyclovir, but this prophylaxis prevents the occurrence of other STIs, which reduces the chances of HIV infection.

The chances of infection increase with concomitant STIs. In this case, damage to the mucous membranes and skin is observed [83; p. 56-67]. Likewise, with intimate contact with an HIV-infected person with the possibility of open wounds or damage to the mucous membranes, accompanied by the presence of microtraumas and ulcers of the mucous membrane. [142; p. 1-5]. Women are more susceptible to

infection due to physiological and anatomical features, as well as the prolonged presence of biological fluids in the vagina [159; p. 814-817].

There is a possibility that ART therapy protects against cervical neoplasia and reduces the incidence of human papillomavirus lesions and prevents recurrent cervical pathologies. [155; p. 5432-5543].

In the absence of regular use of ARV, the infection develops resistance to this therapy [148; pp. 1266-1273]. This immunity is formed by reducing the susceptibility of target cells. Immunity can also arise against the background of changes in the virus genome, forming acquired resistance or transmitted during infection to healthy people (primary transmitted resistance.) [133; pp. 34-43]. This immunity of the virus causes low efficiency of ARV therapy.

According to the Methodological Recommendation “Determination of HIV sensitivity to drugs”, the ineffectiveness of ART therapy was established due to a violation of the regularity of administration, absorption of the drug or transmission of a virus resistant to ART therapy. [147; p. 765-775] On the one hand, part of the HIV “hides” in “hidden reservoirs”, where the concentration of drugs is lower and where active reproduction does not occur, where it can exist for years [134; p. 2183-2191]. Such “shelters” include, for example, “dormant” (latent) CD4+ lymphocytes and follicular dendritic cells in lymphoid tissue.

Thus, according to research data, inflammatory processes of the female reproductive system in women with the human immunodeficiency virus are determined by the abundance of pathogens. But in world sources, no information was provided on the course and methods of treatment of the inflammatory process in HIV patients.

Data on sexually transmitted diseases in HIV-positive women vary. The main emphasis was placed on the treatment of cervical diseases, which are the main factors of fatal outcomes in this group of people, as well as genital inflammatory processes. It is because of this that further research is needed into the effectiveness of ART in this category, which is the subject of this work.

CHAPTER II . MATERIALS AND METHODS OF RESEARCH

Clinical characteristics of the examined women

The work was carried out over 3 years (2018-2021) in cooperation with the AIDS Center outpatient clinic, the gynecology department of the Regional Perinatal Center, and the Bukhara Reproductive Center. A total of 315 patients aged 15 to 41 years were examined. Clinical and laboratory data of 200 patients were analyzed retrospectively for 2018-2019 (comparison group), 115 patients were monitored during 2020-2021 (main group).

In order to verify the information we need while performing our research, we reviewed the medical records of women in labor and pregnant women (form 111/u) registered with women's health centers, as well as their medical history (form 025). The examinations were conducted in accordance with the regulations in force under the order of the Ministry of Health of the Republic of Uzbekistan (Decree of the President of the Republic of Uzbekistan; 11/08/2019; No. PP-4513). Pregnancy management in women who were found to be HIV-positive during the examination was conducted in accordance with the regulatory documents (Resolution of the President of the Republic of Uzbekistan No. PP-3800 dated 06/22/2018 - "On additional measures to prevent the spread of the disease caused by the human immunodeficiency virus, as well as preventing the spread of nosocomial infections"). Women in the main group took ART based on protocols that were grouped into a program to prevent the spread of HIV infection in the Republic of Uzbekistan for 2018 (Appendix to the Resolution of the President of the Republic of Uzbekistan dated January 25, 2018, No. PP-3493).

During the work, the following criteria were taken into account among the subjects:

Age of patients (18-40 years)

Confirmed diagnosis of HIV infection, which was based on examination data, anamnesis, antibodies to HIV infection, the presence of CD4+ leukocytes)

The ability of patients to undergo a full examination and testing during the study

Signs of the onset of development of inflammatory processes in the pelvic organs and external genitalia.

Patients with confirmed HIV-infected status were systematized and grouped based on the classification of V. U. Pokrovsky by stage of the disease, proposed in 2000.

The determination of the degree of HIV infection was based on the duration of the disease, anamnestic status, laboratory data and clinical examination. In general, it is possible to distinguish V stages of HIV infection development, proposed in the classification by V. U. Pokrovsky:

1. Incubation stage. This is the period from the moment the virus enters the body until its first manifestations. Its duration is determined by the individual characteristics of the body, and lasts on average from 2 weeks to 3 months.

2. Stage of primary manifestations. It consists of two subtypes: (IIA and IIB. Stage IIA excludes any pathological manifestations of the disease, and includes only the process of antibody formation. II B, in turn, is an acute stage of HIV infection , in which there are no concomitant and secondary pathologies. During stage II B, an acute course of the disease is observed with the addition of such concomitant pathologies as: fungal lesions of the oral cavity and genitals, herpes diseases, tonsillitis, pneumonia of bacterial etiology, which are easily cured. This period lasts 2.5-3 weeks.

3. Latent period. Characterized by slow progression of immunodeficiency. The characteristic expression and symptoms of which are enlarged lymph nodes, but its manifestation is less common **.** This stage can last from three to twenty years, but on average it lasts about 4-8 years. The level of CD 4+ leukocytes in this stage gradually decreases.

4. Stage of manifestation of secondary diseases. leading to the death of CD4+ leukocytes and progression against the background of this immunodeficiency. The entire symptom complex of developed secondary diseases can be reversible

against the background of treatment and prevention. Depending on the level of damage, several stages are distinguished in stage 4:

IV "A" - the addition of secondary bacterial, fungal and viral pathogens, which may result in dysfunction of organs such as the respiratory system, mucous membranes and skin.

IV "B" - weight loss, disturbance of the nervous system in the periphery and internal organs and more serious skin lesions such as Kaposi's sarcoma.

IV "B" - the addition of secondary diseases that threaten the life of patients.

The fifth (V) stage is the terminal stage, in which damage to organs and systems is observed, which cannot be treated and become irreversible. The effect of treatment at this stage is very low, and death of patients is observed soon after a couple of months.

It is also worth noting that in this study there were no patients at stage IV HIV infection, due to the severity of the terminal condition and the impossibility of complete data collection (Table 2.1).

From the group of patients at stage II of the disease, we identified only patients at stage II A and II B. When diagnosing them and collecting analyses and materials, we did not divide stage II into smaller substages, since stage II is characterized by common clinical manifestations. During the study, we also did not identify patients with stage IVB of development. Therefore, we did the same with the group of patients who are suffering from stage IV of the disease, or rather, combining all the small leads into one common group IV .

Table 2.1

Clinical course of HIV

No.	Diagnosis	Comparison group (n=200)		Main group (n=115)	
		Abs	%	abs	%
1	I Clinical stage	76	38	40	34.8
2	II Clinical stage	84	42	50	43.5

3	III Clinical stage	32	16	20	17.4
4	IV Clinical stage	8	4	5	4.3

The control group consisted of 30 healthy women who visited specialists for a preventive examination or to choose a contraceptive method.

Each patient had a medical record of clinical and laboratory studies opened, in which anamnesis data, history of previous illnesses, information on the strategy of treatment of patients and their outcomes were entered. All patients were informed and gave written consent to participate in this study. Also, all women were consulted about the conduct of therapy and prevention of HIV infection vertically, regardless of the presence or absence of ART.

The group of prospective observation female patients (n = 115) was divided into subgroups: those receiving ART (86% n = 99) and those not receiving ART (14% n = 16). All patients are citizens of the Republic of Uzbekistan. ART was carried out in accordance with the recommendations adopted by the Ministry of Health of the Republic of Uzbekistan. The regimen was selected in accordance with the order of the Ministry of Health of the Republic of Uzbekistan No. 277 of April 30, 2018 "On the implementation of national clinical protocols for HIV infection into practice": This order regulates the implementation of 14 national clinical protocols in medical institutions in all areas of medical services for HIV-infected individuals, including ART, adapted on the basis of WHO protocols and recommendations. TDF / 3TC (300/150 mg) or TDF / FTC (300/200 mg), 1 tablet daily orally. Alternative schemes: AZT + 3TC + EFV (or NVP); TDF+ 3TC (or FTC) + DTG; TDF+3TC(FTC)+NVP.

Based on the results of immunological and clinical studies, it is necessary to correctly prescribe ART to individuals at stages 2B, 3, 4 and 5 without relying on the indicators of the number of CD+4 lymphocytes and PCR of the human immunodeficiency virus Ribonucleic acid in the blood (A1);

- patients whose CD+4 lymphocyte count is less than 350 cells per microliter, regardless of the stage of the disease (A1)

- persons with CD+4 lymphocyte counts that range from 350-499 cells per microliter (B2): patients with PCR of the human immunodeficiency virus ribonucleic acid more than one hundred thousand copies per milliliter; patients over 50 years of age; persons with chronic liver disease (hepatitis C); persons with chronic kidney disease.

Regardless of the current stage of the disease, the level of CD+4 lymphocytes and the number of PCR ribonucleic acid of the human immunodeficiency virus (B2);

- persons with chronic hepatitis B;
- patients with tuberculosis;
- persons with chronic kidney disease;
- persons who have cognitive disorders;
- the presence of anemia and platelet deficiency caused by HIV infection
- pregnant women
- persons undergoing treatment that suppresses the immune system: radiation therapy, cytostatics, CTG

LABORATORY AND INSTRUMENTAL RESEARCH METHODS

The assessment of the condition of HIV-infected women was carried out based on the data from anamnesis collection and objective examination.

Laboratory methods included general and biochemical blood tests, general urine tests, the presence of human immunodeficiency virus RNA in blood plasma using the PCR method, as well as the immunofluorescence method.

Instrumental research methods included PAP test of smears from the cervical canal, colposcopy, and ultrasound of the pelvic organs.

During the examination and collection of research materials, the patients we examined underwent general clinical examinations, including a complete blood count, general urine analysis, blood group and Rh factor, hemostasiogram, biochemical studies, including determination of the level of albumin, creatinine, glucose, ALT, AST, bilirubin, as well as immunological studies, which included diagnostics of hepatitis, antibodies to treponema, the presence of sexually transmitted infections by the PCR method. A certain sequence of examination of patients with HIV infections was carried out in the following order:

Social history of patients with HIV infection.

General information.

1) Passport details, age

2) Education

3) Place and conditions of work

4) Address and living conditions

5) Duration of the disease

6) The way the virus was identified (accidentally or by deliberate examination)

7) Source of infection

The gynecologists performed a cervical canal smear test, an ultrasound of the pelvic organs, a colposcopy and a general examination using mirrors.

In order to diagnose the infectious status, microscopy of vaginal discharge, cytology of smear (PAP test), and bacterial culture of smears were performed.

Collection and analysis of Pap smear results was based on the Bethesda system, which was established in 1999 by the US National Cancer Institute.

The colposcopy examination was performed with a SOM-52 colposcope based on the KAPS system, which allows for a 10-fold increase in the field of view of the object being examined. The interpretation of the colposcopy results was carried out in accordance with the international classification of the International Association of Uterine and Cervical Canal Pathologies, which was supplemented in Barcelona in 2003. The analysis of smears and scrapings of the cervix was carried out based on modern bacterioscopic and culturing methods.

Laboratory diagnostics of T. vaginalis was studied by bacterioscopic method according to Gram, which was based on the use of Johnson-Trasel medium (liver broth and the system " ORION " Finland). Specific IgG were determined by ELISA method based on the system " TrichomonoBest - IgG - strip ". Determination of antigens of C. trachomatis was carried out by PIF method taking into account the influence of monoclonal antibodies to species-specific protein irradiation using the test system "CHLAMONOSKRIN" (RUSSIA).

The determination of special forms of IgA and IgG was carried out by the ELISA method based on the Vector system. Best " and " ChlamiBest " " ChlamiBest HSP -60- IgG ».

The detection of M. hominis and U. urealyticum was based on the use of the PIF method of labeled antibodies, using the system " UREASCAN " " MICOSCAN " (Russia). The process of determining mycoplasmas was based on the use of the test system Mycoplasma Duo 62740 manufactured by " SANOFI DIAGNOSTICS PASTEURS » (France). The process of identifying ureaplasmas was based on the use of selective media «Ureoplasma-96» of the Research Institute of Dermatology and Venereology of the Academy of Medical Sciences of Ukraine and EM named after Pasteur (St. Petersburg). Bacterial culture from a smear isolated from the cervix area was performed on the Sabouraud and Chapek medium. Identification of spore-

bearing fungi was carried out taking into account the criteria of morphological and cultural properties, more precisely, taking into account the growth rate, type of structure, using agar. Description of the isolated bacteriological cultures from the cervical canal was based on Gram bacterioscopy, and their identification was carried out using the identification kit of JSC « Lachema » (Czech Republic). All diagnostic methods were carried out strictly, based on the protocols attached to the test systems.

1. Immunological research methods

When examining the protective state today, they have a general examination of all protective mechanisms. This study is based on the study of cellular and humoral protective response, the number of cytokines, non-specific protective reactions.

2. Definition of cellular immunity

All patients we studied gave blood from the cubital vein to determine the protective function. Blood was collected in a centrifuge tube, pre-treated with heparin solution (V = 5-10) μl was isolated to determine the number of white blood cells and lymphocytes by adding the dye of S.I. Zadorozhny and I.M. Dozmorov (1987). Isolating monocytes from the collected blood by taking the Ficoll-Verografin gradient density of 1.077 g/ml, using the Boyum method (1968). The number of white blood cells was counted in a Goryaev chamber using the classical method and the concentration of lymphocytes was brought to $2x10^{6}$ in 1 ml. Using the trepan blue test (0.1%), we determined the viability of lymphocytes.

3. Determination of the subpopulation composition of lymphocytes

The results of the state of the protective system were assessed using the activation of differentiation antigens of the SD. The markers of the ICC were determined: SD+3, SD+4, SD+8, SD+16, SD+25, SD+95 and SD+71 lymphocytes. The activation of SD receptors was carried out using the rosette formation reaction, which is carried out by monoclonal antibodies of the " LT " class manufactured by Sorbent LLC, Russia, according to the method of Garib F.Yu. et al. (1995)

4. Determination of immunoglobulin levels

Ig of the three main classes A, M, G in the blood serum was carried out according to the principle of solid-stage enzyme immunoassay using the tests of the systems of JSC Vector Best (Russia), using the manufacturer's instructions. The results are recorded in g / l.

5. Determination of phagocytic activity

Phagocytic expression of white blood cells was studied according to the principle of Kudryavtseva V.V. (1984) by introducing a mixture of white blood cells and latex particles into a thermostat at a set temperature of 37C for 25 to 30 minutes. The number of neutrophils that phagocytized the latex particles was counted. The results are expressed as %. Melamine-formaldehyde latex with a diameter of 1.5 microns (Research Institute of Biological Instrumentation, Moscow) was used in the experiment.

§ 2.2.6. Determination of cytokine status

Determination of the concentrations of cytokines IL -4, IL -8, IL-17/A and IFN -γ was performed in blood serum using the solid-phase enzyme immunoassay method in accordance with the manufacturer's recommendations (Vector Best LLC, Novosbirsk, Russian Federation). The result was expressed as a number in pg/ml.

7. Determination of the level of complement component C3 and C-reactive protein

To determine the C3 component of complement and C-reactive protein in the blood serum of the control and main groups of women, the solid-phase ELISA method was used using a test kit manufactured by Cytokine LLC (RF) according to the attached instructions. The results were expressed in ng/ml.

STATISTICAL PROCESSING OF THE RECEIVED DATA

On a Pentium - IV personal computer, thanks to the Microsoft software package OfficeExc e l -2003, using in combination the built-in functions of statistical processing and « Biostatistics » for Windows (version 4.03), the data obtained during the research were subjected to statistical analysis. Methods of variation parametric and nonparametric statistics were applied taking into account the arithmetic mean of the studied result (M), standard deviation (σ), classical error of the mean (m), relative values (frequency, %). According to the Student criterion (t) with calculation of the chances of error (P) in the analysis of the normality of distribution (according to the excess criterion) and equality of common variances (Fisher's F - criterion).

CHAPTER III. ANALYSIS OF SOMATIC AND REPRODUCTIVE HISTORY IN FEMALE INDIVIDUALS WITH INFLAMMATORY DISEASES OF THE PELVIC ORGANS AGAINST THE BACKGROUND OF HUMAN IMMUNODEFICIENCY VIRUS

The current situation with HIV infection, which poses a pandemic threat, can be put on a par with world wars in terms of both the number of fatalities and the damage it causes to society. The problem with HIV infection is especially relevant for women during the reproductive period of life, since it poses a threat to children born to sick mothers. Experience and clinical practice accumulated over the years have significantly changed the course of this infection. Based on modern medicine, patients with this infection are no longer considered incurable and HIV is currently a chronic, long-term, and controllable disease. This achievement has become possible based on the studies of HIV infection, and most importantly, the development and introduction of antiretroviral therapy (ART) into clinical practice (Pavia C. , Navarra

A. , Pisani G. , 2006). After the discovery and introduction of ART, the unthinkable happened: within a couple of years, the disease changed its status from fatal to chronic, controllable by means of therapy. Nowadays, HIV-infected people are no different from healthy people, they live, work and are socially adaptive. Recent studies have shown changes in the social and gender composition of HIV carriers, the incidence rate of females has increased, the infection has begun to be detected not only in people from unfavorable environments, but also in the population whose social status is above average, the group of infected people whose age is above average is growing, and the heterosexual route of infection has also increased (Ibrahim F. W. Schembri G. , Taha H. , 2009). The chronicity of the disease and the emergence of the possibility of maintenance therapy have set new tasks, namely: establishing high-quality medical care, maintaining the quality and fullness of life of patients with HIV infection. In this task, one of the main elements is the restoration of the reproductive function of patients with HIV infection and the prevention of vertical transmission of the disease to both the partner and children. Such a result is possible with proper monitoring of patients, adherence to the rules of antiretroviral therapy and the right benefits for achieving pregnancy (Hoffman . C. , Mulcahy F. Rockstroh B. Kamps , 2006) Many aspects of this problem such as the influence of ART therapy and HIV infection on sexual function, the quality of gametes of males and females, the probability of pregnancy are not yet clear. And of course, the influence of population data on the nature and frequency of accompanying inflammatory pathologies of the reproductive system .

This chapter will consider a detailed analysis of the clinical picture of HIV infection in females. A total of 315 females aged 15 to 41 years were examined. Clinical and laboratory data of 200 patients were analyzed retrospectively for 2018-2019 (comparison group), 115 patients were monitored throughout 2020 (main group). 30 women with negative HIV indicators were selected as a control group. Concomitant diseases in the acute stage were excluded.

The average age of patients in the comparison group was 38.6±0.67 years , in the main group 35.1±0.65, in the control group 34.93±1.50 years, $p \leq 0.05$. The data

obtained during the study confirmed the fact that the incidence of HIV infection among young people of active and reproductive age is the highest. The study also proved that the age group of patients with congenital HIV infection has increased, which indicates the effectiveness of ART therapy and leads to an increase in the average life expectancy of patients.

We also assessed the social status of the subjects from the two groups. A number of characteristic features were identified when comparing the educational level of the subjects (Table 3.1).

The percentage of women with secondary and secondary specialized education was significantly higher in the examined women of both groups compared to women with higher education. In the course of assessing the profession of the subjects, we took into account the risks and possible impact on the development of the main pathology as a result of exposure to factors, as well as conditions of professional activity. The overwhelming majority of HIV-infected women are housewives or temporarily unemployed.

Table 3.1.

Social history of retrospective and prospective examined women, abs/%

Indicator	Comparison group (n=200)	Main group (n=115)	Control (n =30)
Education			
Higher	32/16	16/13.9	10/33.3
Secondary specialized	127/63.5	62/53.9	11/36.7
Average	41/21.5	37/32.2	9/30
Social status			
Works	55/27	31/27	15/50
Temporarily out of service	34/17	17/14.8	6/20
Student	0	0	0
Housewife	111/55.5	67/58.2	6/20
Other	0	0	3/10

Place of residence			
City	106/53	65/56.5	20/66.6
Village	94/47	50/43.5	10/33.3

Strong differences between the groups were excluded during the assessment. Information about marital status in the two groups did not differ and most of the HIV-infected subjects were not married (58.5% in the comparison group and the main group), and among the healthy subjects, all were married. Among the women under study, it should be emphasized that in the group of subjects who did not receive therapy, the number of unmarried women was significantly higher compared to the patients who were observed and receiving ART, - 35 (41.1 ±5.3%) and 18 (24.0 ±5.0%), ($p < 0.05$), it was also indicated that all relationships were completed after the diagnosis of HIV infection - among the subjects, their number was 10 people (13.3 ±3.9%) and 32 (37.6 ±5.2%) women in the comparison group. Women whose goals were to give birth to a healthy child and preserve the integrity of the family, considered themselves capable of providing for and successfully raising children. Their desires were confirmed by the fact of social stability. Of the bad habits in the comparison group, 20% noted smoking and 20% - regular alcohol consumption, in the main group - 25.2 and 22.6%, respectively. When analyzing the husband's morbidity, the following was noted - in the comparison group, 64.5% of those examined had uninfected husbands, in the main group - 54.5%.

The route of infection in 40% of cases in the comparison group and in 43.5% is sexual, it should be noted the high percentage of unknown route of infection in 46.5% and 40%, respectively (Table 3.2). 27 (13.5%) patients in the comparison group and 19 (16.5%) women in the main group were infected parenterally.

According to the subjects, the cause of infection was the use of narcotics, although each of the subjects does not consider themselves drug addicts, citing the fact that the infection occurred in adolescence with a single or accidental use of narcotics.

Table 3. 2.

Routes of infection for women

The way a woman gets infected with HIV	Comparison group (n=200)		Main group (n=115)	
	abc	%	abc	%
Sexual	80	40	50	43.5
Parenteral	27	13.5	19	16.5
Vertical	0	0	0	0
Unknown	93	46.5	46	40

The duration of HIV infection among the examined retrospectively was: 1 year in 10.5% of the examined, 2 years - 10%, 3 years 17% and more than 3 years - 62.5%. Infection of most patients fluctuates in the period from one to three years. The number of infected in the comparison group less than one year ago is 15.8%, more than ten years - 11%, in the main group these values are 18 and 12%, which does not affect the integrity of the statistical picture. It is concluded that women with recently diagnosed infection are registered more often than others. At the same time, the majority of those registered were detected by immunoblot less than 1 year ago, which proves an increase in the transmission of HIV infection through sexual contact.

Also, it should be noted that there were bad habits among the examined patients. Thus, alcohol abuse was noted by 20% of patients from the comparison group and 23% of patients from the main group.

Of the concomitant somatic pathologies, arterial hypertension was observed with approximately the same frequency in both comparison groups (Figure 3.1). Mild and moderate iron deficiency anemia was observed in every fourth patient. Gastrointestinal diseases were observed in every sixth patient, and the frequency was lower than in the control group, which is probably due to the rare referral of this category of patients to somatic hospitals, $p < 0.05$. An ophthalmologist was observed

in 5% of patients from the comparison group and 4.3% of those from the main group. Thyroid pathology, represented by diffuse goiter with / without thyroid dysfunction, was observed in 8.7% of cases in the main group and in 8.5% of cases in the comparison group. Surgical pathology - appendectomy - was noted in the anamnesis of 5% of patients in both observation groups. We noted a lower frequency of general somatic pathology in the examined patients, possibly due to the rare frequency of seeking medical attention due to the presence of the underlying pathology.

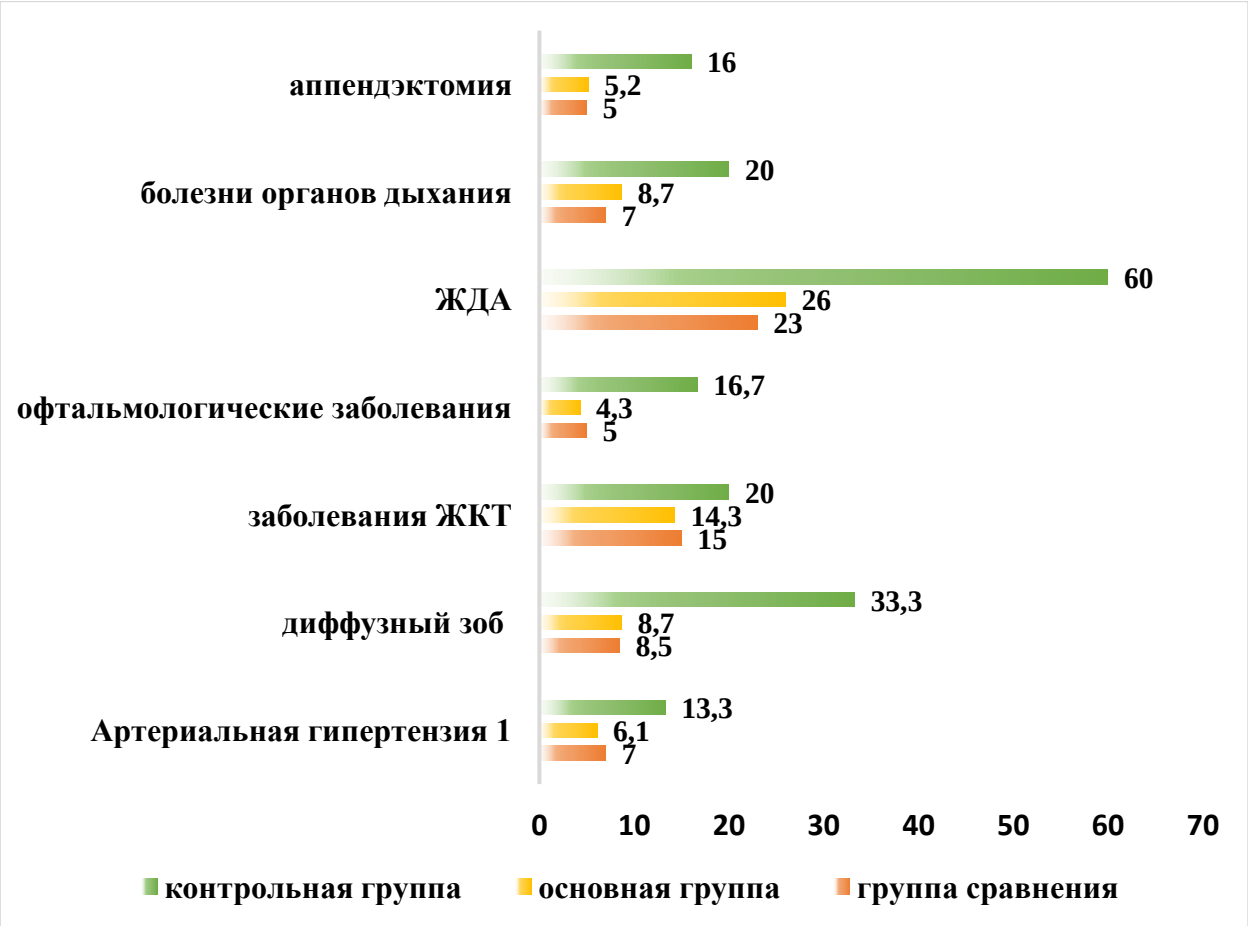

Figure 3.1. Somatic pathology in those examined (%)

The following results were obtained in the analysis of the reproductive function. One pregnancy in the anamnesis was observed in 9.5% of patients in the comparison group, in 9.6% of the main group, two pregnancies were observed in 63 and 63.5% of the examined women, and more than three pregnancies were observed in 23% and 22% of the women. On average, more than 66% of the examined women in both groups gave birth 2 or more times. During pregnancy, 29% of the patients in the comparison group and 28% in the main group had acute respiratory viral

infections, viral hepatitis (B, C) was noted in no more than 3% in both groups. Iron deficiency anemia of grades 1-2 was detected in 75% of the patients in the comparison group, while it was 64% of the women in the main group in relation to the control group of the examined women - 50%.

About 65% of subjects from the comparison group and 87% of those from the main group undergo ART. Antiretroviral therapy is received by 85.5% of patients from the comparison group and 86% of those from the main group. The duration of etiopathogenetic therapy in the comparison group is as follows: 1 year - 21% of patients, 2 years - 9%, 3 years - 20% and more than three years - 50%, in the main group - for 1-2 years received 10.5% of patients, for 3 years - 16.6%, more than three years - 62.4%.

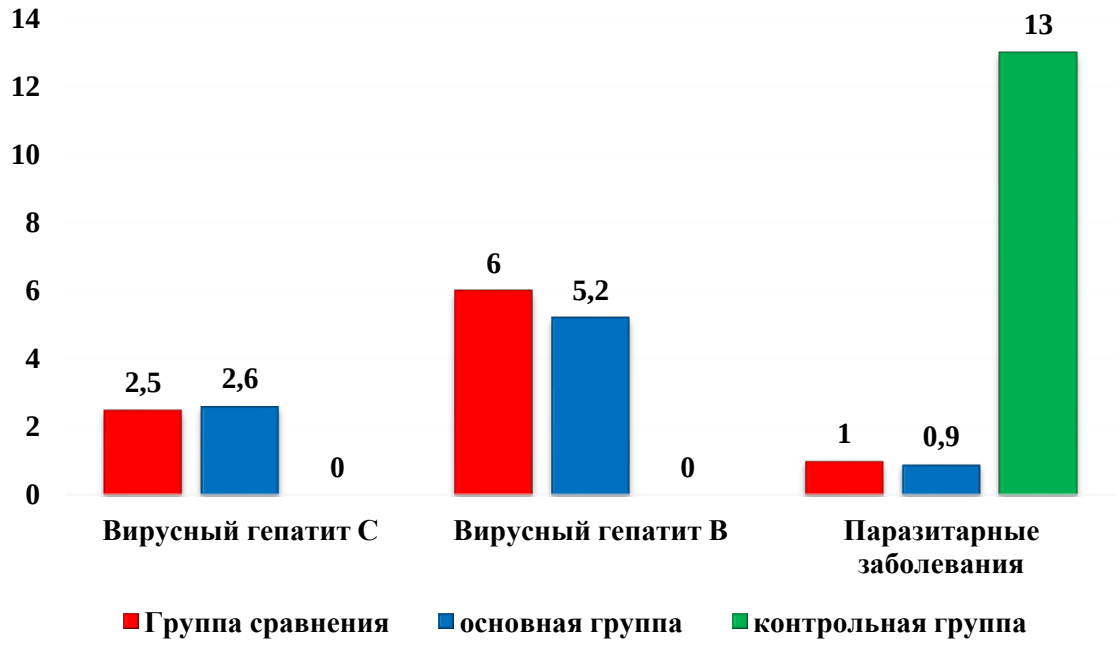

Figure 3.2. Infectious diseases among those examined (%)

It should be noted that viral hepatitis B was present in 6% of cases in the comparison group and in 5% of cases in the main group (Figure 3.2), which had a reliable difference compared to the control values ($p<0.05$). Viral hepatitis C was encountered 2 times less frequently. People who were aware of their illness and did not undergo treatment courses cited the high cost and duration of drug intake. Parasitic diseases were noted rarely compared to the overall incidence and in relation to the control group.

As a complication of the underlying disease, our patients noted "chronic" diarrhea in 21% of cases (n = 42) from the comparison group, 22.6% (n = 26) from the main group, relapses of upper respiratory tract infection were noted by 23% (n = 46) and 23.5% (n = 27), respectively. Periodically occurring hyperthermia was noted by 6.5% of patients (n = 13) from the comparison group and 8% (n = 9).

The establishment of menstrual function in the examined patients proceeded physiologically, which gives grounds to conclude that the initial indicators of the start of functioning of the reproductive system did not deviate from the norm.

According to the nature of menstrual function, the overwhelming majority of those examined (83% of the comparison group and 82.6% of the main group) had a normal menstrual cycle.

IUD carriers are 29% of those examined in the comparison group, 25.2% of those in the main group, compared to 36.7% in the control group; COCs are used by 7.5%: 12.2%: 20%, respectively; barrier methods of contraception are used by 9%: 7.8%: 23.3%; injection methods are used by 4%: 3.5%: 6.7%, DHS in 8%: 7%: 10% of those examined, respectively (Table 3.3).

Table 3.3.

Contraception methods used

Comparison groups	Navy	COOK	Barrier methods	Injection methods	DHS
Main group (n= 115)	25.2%	12.2%	7.8%	3.5%	7%
Comparison group (n = 200)	29%	7.5%	9%	4%	8%
Control group (n= 30)	36.7%	20%	23.3%	6.7%	13.3%

Proliferative processes of the uterus were extremely rare and were represented by uterine myoma, which was diagnosed in 2 patients (1%) from the comparison

group and in 1 (0.9%) from the main group, endometriosis in 2% (n = 4) and in 1/7% (n = 2) of patients, respectively.

To date, there is very little reliable information on the state of gynecological health of HIV-infected women. There are isolated reports that talk about an increase in the incidence of infectious and inflammatory diseases of the pelvic organs, which may be due to chronic immunodeficiency. The 2014 works published by Gafurov Yu. T. show a high incidence of precancerous conditions of the cervix in HIV-infected women, which in the shortest possible time develops into cervical cancer. Gafurov Yu. T. proves that cervical disease occurs in 28% of infected women, and invasive uterine cancer in 11% of cases, which allows us to classify infected people as a group of people with a high probability of developing severe cervical conditions.

The main reason for visiting a gynecologist is discharge from the external genitalia, itching, burning in the vulva; dysuric disorders, dyspareunia, deterioration of the psycho-emotional state, which was assessed as an inflammatory process of the lower genital tract and confirmed by vaginal smear data (Table 3.4).

During examination on a gynecological chair with a mirror, a large or medium discharge of a creamy or mucopurulent nature was noted. The vaginal mucosa was hyperemic with erosions, cracks and infiltrates. The severity of symptoms was shown in Table 3.5.

Leukocytosis in cervical discharge in the comparison group averaged 34.16±0.26, in the main group - 34.65±0.18 compared to the control - 14.1±0.1, $p \leq 0.001$. High pH values were observed in 71% (n = 140) of the subjects (pH 6.5±0.5), increased (pH 5.5±0.5) in 32% (n = 60) in the comparison group; in 60% (n = 68) of the subjects (pH 6.5±0.5), increased (pH 5.5±0.5) in 45% (n = 50%) from the main group. Optimal values (pH 3.8-4.2) were not noted in any of the cases.

Table 3.4.

Reason for visiting a gynecologist

No.	Complaints	Comparison group	Main group (n=115)	Control group (n= 30)

		(n=200)					
		abc	%	abc	%	abc	%
1	Discomfort in the vagina	107	53.5*	62	54*	11	37
2	Pathological discharge from the genital tract	70	35	39	34	15	50
3	Pain during intercourse	25	12.5*	15	13*	2	7
4	Itching and burning	26	13	15	13	10	33.3
5	Urination disorder	29	14.5	17	15	4	13.3
6	Discharge mixed with blood from the genital tract	24	12	14	12.2	3	10
7	No complaints	2	1	1	0.9	4	13.3

*Note: *- values are reliable in relation to the control group (p<0.05 - 0.001)*

Table 3.5 .

Intensity of the reason for visiting a gynecologist

Symptoms	**Comparison group (n=200)**				**Main group (n=115)**			
Intensity	1	2	3	4	1	2	3	4
Discharge	9 (4.5%)	110 (55%)	70 (35%)	11 (5.5%)	5 (4.3%)	38 (33%)	54 (47%)	18 (16%)
Itching	24	50	114	12	2	69	33	11

	(12%)	(40%)	(57%)	(6%)	(1.7%)	(60%)	(29%)	(9.5%)
Burning	20 (10%)	52 (26%)	112 (56%)	16 (8%)	9 (7.8%)	28 (24%)	68 (59%)	10 (8.7%)
Pain	18 (9%)	148 (74%)	29 (14.5%)	5 (2.5%)	26 (23%)	49 (42%)	28 (24%)	12 (10%)
Infiltration	5 (2.5%)	71 (35.5%)	35 (17.5%)	89 (45%)	15 (13%)	25 (22%)	32 (28%)	43 (37%)
Hyperemia	0	30 (15%)	159 (79.5%)	11 (5.5%)	17 (15%)	29 (25%)	33 (29%)	36 (31%)
Cracks	74 (37%)	98 (49%)	26 (13%)	2 (1%)	26 (23%)	32 (28%)	24 (21%)	33 (29%)

Since all types of microbiota require different approaches to treatment, it is necessary to determine the quantitative and qualitative composition of associates. Bacteriological culture revealed an increased content of Enterobacterium spp ., Streptococcus spp ., Staphylococcus spp ., as well as a decrease in lactoflora. The etiological factors were: *Staphylococcus* epidermidis, Escherichia coli, *Staphylococcus* hemoliticus. More than 60% of both groups were diagnosed with colpitis, in 23% of cases bacterial vaginosis. The percentage of nonspecific colpitis prevailed - 21.5%, cervicitis and endocervicitis in 55% of cases in the comparison group, in the main group - cervicitis in 47%, chronic endometritis in 3.5% of cases, candidal colpitis in 13% of cases.

According to the structure of the biocenosis in the comparison group with vaginitis, several variants of the state of the biocenosis were identified: absolute normocenosis - in 21% (n = 42), vulvovaginal candidiasis in 25.5% (n = 51), aerobic dysbiosis in 8% (n = 16), obligate anaerobic dysbiosis in 15.5% (n = 31), aerobic-anaerobic dysbiosis in 9% (n = 18) and mixed dysbiosis in 21% (n = 42). Ureaolasma was detected spp . in quantities exceeding 10*4 CFU/ml in 77 (38.5) patients as a possible etiologic agent of vaginitis; in 18 (9%) – HSV type 2. In women from the main group, absolute normocenosis was noted in 20% (n=23), vulvovaginal

candidiasis in 27.8% (n=32), aerobic dysbiosis in 7.8% (n=9), obligate anaerobic dysbiosis in 18.2% (n=21), aerobic-anaerobic dysbiosis in 7.8% (n=9) and mixed dysbiosis in 18.2% (n=21). In 34 (29.5%) patients, Ureaplasma was detected. spp . in quantities exceeding 10*4 CFU/ml, in 11 (9.5%) – herpes simplex virus type 2 (Fig. 3.3).

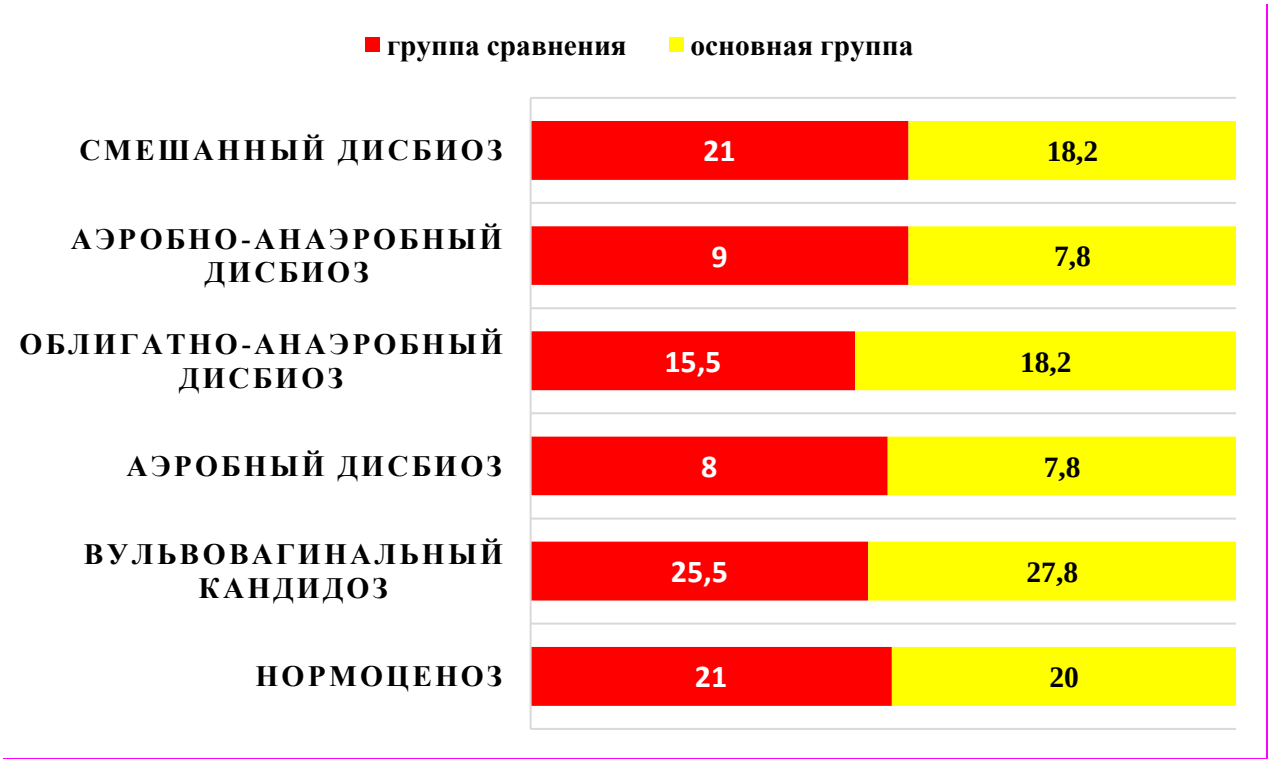

Figure 3.3. Structure of the biocenosis in the examined (%)

During colposcopy, 41% of women from the comparison group and 34% of women from the main group had ectopia of the cervix (Table 3.6). Among the diseases of the cervix in HIV-infected women, cervicitis (53% and 41.7%, respectively) is followed by human papillomavirus (on average 22% in both groups), cervical polyp (12% and 8%, respectively), and mild dysplasia (6% and 4%).

The difference between the number of cervical pathologies in females who were infected with HIV turned out to be statistically significant only for cervical papilloma in comparison with other cervical pathologies, which can be explained by the immunosuppression of the body, which usually develops against the background of HIV infection and increases the risk of cervical infection, in particular, with the papilloma virus.

Among the diseases of papillomavirus etiology that occur in HIV-infected individuals, many authors note almost all forms of pathology: from genital warts to cervical cancer, malignant vulvo -vaginal neoplasia and squamous cell anal intraepithelial neoplasia.

Table 3.6.

Заболевания шейки матки	**Группа сравнения, n=200**		**Основная группа, n=115**		**p**	**Контр. группа, n=30**	**p**
цервицит	105	(53%)	48	(41,7%)*	>0,05	16(53%)	>0,005
эктопия	82	(41%)*	39	(34%)*	>0,05	21(70%)	>0,01
лейкоплакия	23	(11,5%)	8	(6,9%)	>0,05	0	-
папиллома	44	(22%)	25	(22%)	>0,05	0	-
полип	24	(12%)*	9	(8%)*	>0,05	1(3,3%)	>0,001
эндометриоз	14	(7%)*	11	(9,5%)*	>0,05	3 (10%)	>0,05
легкая дисплазия	12	(6%)*	5	(4%)*	>0,05	1(3,3%)	>0,001

*Примечание: *- значения достоверны по отношению к группе контроля (p<0,05 - 0,001)*

Colposcopic picture of the examined

The prevalence of HPV among HIV-infected individuals remains high even in patients receiving active retroviral therapy.

In extremely rare cases, vaginal infection is diagnosed as the only gynecological disease, since this inflammatory process is always accompanied by the involvement of the cervix, which in turn is the second line of defense of the reproductive system in women. At this stage, the destruction of pathogenic and transient microorganisms is observed. Sexually transmitted infection (Chlamydia trachomatis , mycoplasma genitalium, etc.), is the strongest aggressor that affects the mucous membrane of the cervix. Mycoplasma was recognized as an absolute

pathogenic flora genitalium , as it causes inflammation of the genitourinary organs with pronounced clinical symptoms.

PCR testing of endocervical scrapings in the examined women revealed monoinfection in an average of 18% (36/18) of cases and mixed infection in 81.4% (36/18). These patients complained of heavy vaginal discharge (58.2% of the comparison group (n = 23) and 61% of the main group (n = 11)), unpleasant odor (25.5% and 31.4%), itching (10.9% and 14%), and burning (67.3% and 72%) in the vagina. Chlamydia trachomatis was detected in 24% of the comparison group, Mycoplasma hominis and M. genitalium – in 4.5 and 6.3%, respectively; Ureaplasma urealyticum, U. spp. and U. parvum – in 10.7, 51 and 28%, respectively; Herpes simplex virus – in 27% and Human papilloma virus 16 and 18 serotypes – in 22% of women. In patients of the main group, we observed the following: Chlamydia trachomatis was detected in 19% of those examined in the comparison group, Mycoplasma hominis and M. genitalium – in 7 and 5.2%, respectively; Ureaplasma urealyticum, U. spp. and U. parvum – in 15, 48 and 23%, respectively; Herpes simplex virus – in 31% and Human papilloma virus 16 and 18 serotypes – in 22% of those examined (Fig. 3.4).

Based on the data from the studies conducted, it is worth noting the importance of testing for oncogenic HPV types in people suffering from HIV infection, since there is a combination with cervical diseases in almost 100% of cases.

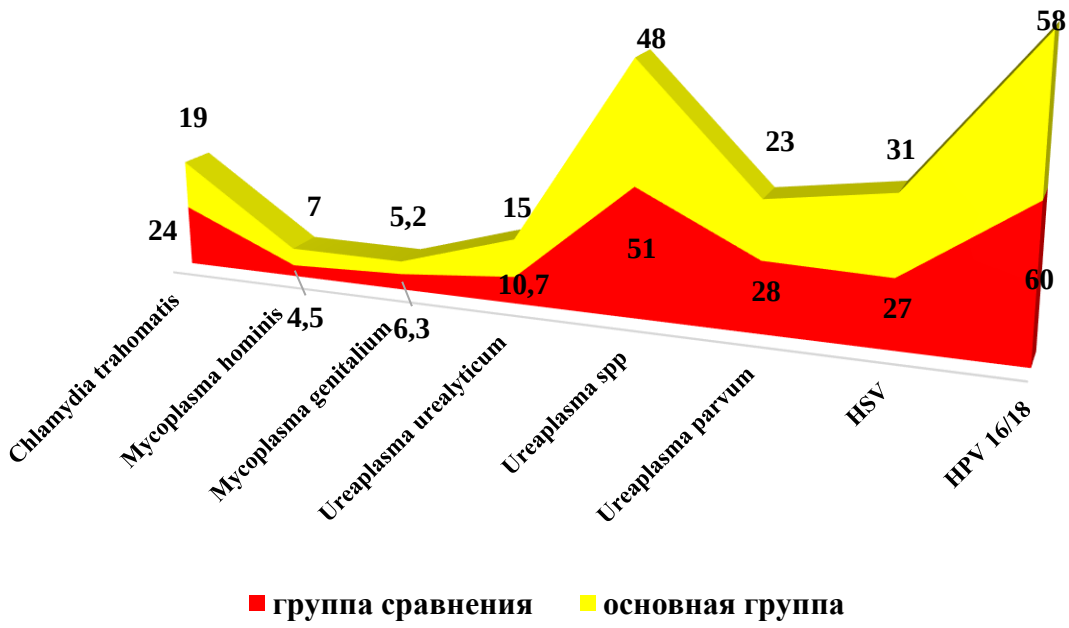

Figure 3.4. PCR scrapings in those examined (%)

Polymicrobial associations, which are the causative agents of non-specific vaginitis and cervicitis, include bacteria such as Chlamydia trachomatis , trichomonas vaginalis , mycoplasma genitalium , mycoplasma hominis and conditionally hostile flora. Ineffectiveness of therapy is observed due to a large number of etiological factors, which in turn leads to an increased incidence of various complications, an increase in the number of strains that are resistant to antibiotics, as well as chronicity of the process with subsequent relapse. Due to ignorance of antibiotic resistance and etiological factors, relapses of nonspecific vulvovaginitis are observed against the background of antibacterial treatment. With complex treatment with local antibiotics, the situation is often aggravated, increasing the deficiency of lacto- and bifidoflora of the vagina.

In conclusion, it can be concluded that HIV-infected women belong to the group of the active reproductive period, who intend to maintain their reproductive health and, in most cases, further conception of children. Having education and work, these individuals form a stable social group of people. Most of them live in families, 65% of which have the ability to fully support their children. The main route of transmission of infection is heterosexual, in 25% of females the cause of infection is

the use of drugs, although they themselves do not consider this to be the cause. The duration of infection for more than 3 years is noted in 62.5%. ART therapy is received by about 86%. An increase in the average age of HIV patients who need specialized gynecological care is also noted. It is worth noting that 2/3 of the infected were examined in a gynecological bed for the first time.

Purulent-inflammatory diseases of the cervix are the most common reasons for hospitalization in a gynecological bed. It should be taken into account that 35% of patients were hospitalized repeatedly, among them about 25% due to relapse of the disease. Condylomas were detected in 49% of cases in diseases of the external genitalia, it is worth considering that 65% of them were hospitalized with a relapse of this pathology. HPV with a high probability of transition to oncology type 16 was detected in 100%, type 18 was detected in 45% of those examined with CIN , which gives reason to consider the human papillomavirus as the cause of diseases of the cervix and external genitalia in patients with HIV infection. In patients with inflammatory diseases of the pelvic organs, laboratory diagnostics of blood did not record the presence of an inflammatory process.

Optimal biocenosis was not detected in any of the subjects from the samples taken from vaginal discharge. Colpitis was diagnosed in more than 60% of both groups, bacterial vaginosis in 23%. The percentage of non-specific colpitis prevailed - 21.5%, cervicitis and endocervicitis in 55% of cases in the comparison group, in the main group - cervicitis in 47%, chronic endometritis in 3.5% of cases, candidal colpitis in 13% of cases. During the studies, sexually transmitted infection pathogens were detected in half of the patients (49%). Late diagnosis and initiation of treatment lead to the transition from the acute stage to the chronic stage with concomitant aggravation of the disease. When conducting PCR testing of endocervical scrapings in the examined women, monoinfection was detected in an average of 18% (36/18) of cases and mixed infection in 81.4% (36/18). In both groups, there were cases of determining opportunistic flora in a titer that can be diagnosed and also respond to antibiotic treatment without complications. Frequency of Ureaplasma spp . in titers over 105 GM/ml was practically no different in the HIV-infected group, as in the

control group, and in the main group. In contrast to the above, the frequency of occurrence of Candida spp . was determined 1.5 times more often than in the comparison group. This phenomenon is explained by the effect of the virus on the immunity of this group.

CHAPTER IV . CHARACTERISTICS OF IMMUNE SYSTEM PARAMETERS IN WOMEN WITH INFLAMMATORY DISEASES OF THE GENITALIA AGAINST THE BACKGROUND OF HUMAN IMMUNODEFICIENCY VIRUS

The development of an immune response to viral infections is a complex and multi-stage process, during which such protective factors as cellular and humoral immunity participate. The response of cellular immunity to inflammation in the genital tract in females characterizes the degree and form of the disease with its subsequent probabilities of relapse. It is worth noting that the facts of the pathogenesis of the formation of an immune response in the concomitant course of HIV infection are poorly understood. Such a duet leads to strong comprehensive changes in the protective reaction, which leads to a variety of clinical pictures. Even with knowledge in the field of humoral and cellular protection of people with inflammatory genital diseases (IDG), the progress of the protective status at the stage of preventing the inflammatory process in the genital organs in women still remains poorly understood.

Based on this, we conducted a dynamic study of the protective mechanism, both innate and acquired, together with the study of the cytokine status. A group of prospective observation patients (n = 115) with an inflammatory process of the genital organs was divided into two subgroups - Group 1 consisted of 99 women who received ART (86%), Group 2 consisted of 16 women who did not receive ART (14%). The results obtained were compared with the indicators of 30 healthy women in the reproductive period.

CHARACTERISTICS OF INNATIVE IMMUNITY INDICATORS IN THE EXAMINED WOMEN

Inherited immunity is the ability of the body to fight pathological (microbes, poisons, atypical cells, viruses) elements found in the body . The innate defense mechanism consists mostly of myelocytes, there is no specificity to antigens, no replicant response, no function of remembering the first interaction with foreign antigens. These mechanisms work throughout life and have a quick response. Subsequently (after 4-5 days), a specific and very effective chain of adaptive defense mechanism joins the confrontation with the foreign agent.

To determine the state of innate immunity in HIV-infected women with inflammatory process of genital organs, we studied quantitative content of natural killer cells (CD 16+), phagocytic activity of neutrophils, concentration of complement C3, level of CRP and IFNγ . As can be seen from Table 4.1. relative level of CD 16+ cells in women of group 1 was lower than values of control group and amounted to on average 12.6 ±1.4% against 13.7 ±1.1% in control ($p < 0.01$), while in women of group 2 level of killer activity was reliably reduced (9.7 ±1.1%) relative to control group, ($p < 0.05$) and 1.3 times lower than values of group 1, ($p < 0.001$). The same dynamics were observed in relation to absolute values of CD 16+ cells, ($p < 0.05$). As is known, CD 16+ or NK cells are natural destroyers (natural killer cells) are a type of lymphocytes related to natural immunity. They have the ability to secrete enzymes that break down cells and fight viruses, as well as atypical cells, participate in the production of cytokines and chemokines.

NK cells are present in large quantities in the body, a large number of them are found in the spleen, liver, peripheral vessels, which makes up from 5 to 20% of the total number, and a smaller number are found in the lymph nodes and decidural membrane of the uterus.

NK cells are short-lived cells, but NK cells have been found circulating in the blood for several months. A reduced level of these cells indicates the presence of an

inactive inflammatory process associated with an excess of infectious pathogen, and thus indicates the chronicity of the inflammatory process.

Таблица 4.1.

Показатели врожденного иммунитета у ВИЧ инфицированных женщин с воспалительным процессом гениталий

Иммунологические показатели	Контрольная группа (n=30)	1-я группа, (n=99)	2-я группа, (n=16)
CD16+, %	13,7 ± 1,1	12,6 ± 1,4^	9,7 ± 1,1*
CD16+, abc	335 ± 19	201 ± 18*^	513 ± 23*
ФАН, %	54,5 ± 1,3	49,3 ± 1,8*	46,5 ± 1,3*
С3комплемент, нг/мл	33,7 ± 1,1	47,3 ± 1,6*^	60,1 ± 1,6*
СРБ, нг/мл	4,8 ± 0,6	7,1 ± 1,0*	12,4 ± 1,1*
IFNγ, пг/мл	24,3 ± 1,4	16,2 ± 1,0*	13,8 ± 0,7*

*Примечание: *Значения достоверны по отношению к контрольной группе*

^Значения достоверны по отношению к данным 2-й группы

(p<0,05 -0.001

Neutrophil phagocytic activity (NPA) is a component of the body's non-specific defense system. The examined women had a reduced level of phagocytic activity, with a more profound deficiency observed in women who were not receiving ART. Thus, on average, women with human immunodeficiency viruses who are taking ART had a level

FAN averaged 49.3 ±1.8 % versus 54.5 1.3 ±% in the control, $p < 0.05$ (Fig. 4.1) . And in women of the 2nd group, the FAN level was lower than the values of the 1st group and significantly lower than the values of the control group (46.5 ±1.3 %), $p < 0.01$. It was noted that patients with impaired phagocytic activity of neutrophils suffer from recurrent infections.

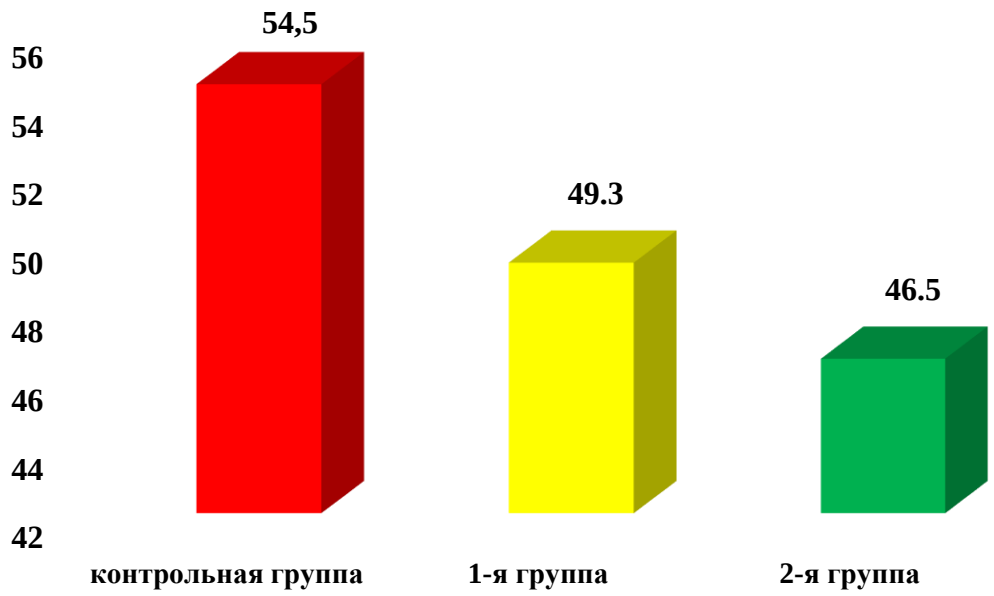

Fig.4.1. FAN level in examined women, %

As a result, in females infected with the human immunodeficiency virus with concomitant inflammation of the pelvic area, inhibition of the absorption properties of neutrophils is observed, while the concentration of natural killers in the representatives of the first group and underestimation in the persons of the second group. These results indicate a breakdown in their generation into adult cells and a violation of the ratio of killers, which, together with a decrease in T-cell control, leads to chronic inflammatory diseases of the genitals.

Complement is a protein system that includes about 20 interacting components. Complement proteins are synthesized mainly in the liver . Under the influence of complement systems, its relationship with the humoral system is observed, which is involved in various inflammatory processes, and as a result, involves these systems in the reaction of the immune-inflammatory response. The main element of the protein breakdown process is C3. Its inclusion due to proliferation is the central component of component activation. As a result of complement system activation, the C3 component is split and its level changes, which causes platelet and neutrophil aggregation.

In our studies, the level of complement component C3 in females with the human immunodeficiency virus and who had undergone ART was significantly

elevated, averaging 47.3 ±1.6 ng/ml, which is 1.4 times higher than the values of the control group, p<0.01 (Fig. 4.2).

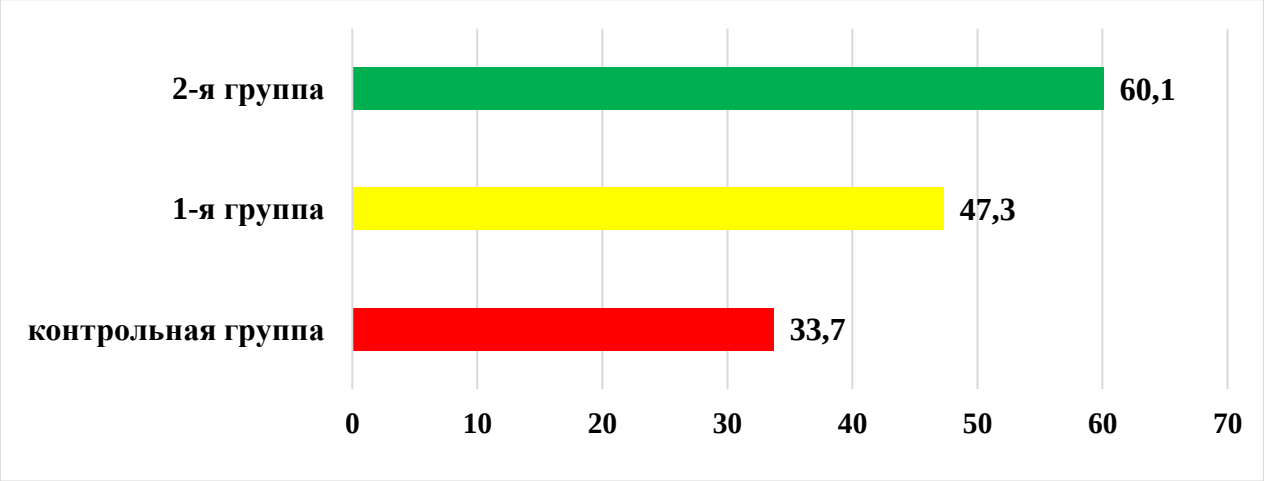

Fig. 4.2. Level of complement component C 3 in examined women

Elevated levels of complement component C3 tend to provoke the movement of neutrophils from the bone marrow, which leads to leukocytosis.

Most of the constituent elements are functional only in a set, but their uninhibited forms exist for a few minutes. If no interaction occurs during this period, the elements become inactive. Thus, in HIV-infected women with inflammatory process of genital organs who did not receive ART, the level of C3 component of complement significantly exceeded the indicators of women of the 1st group (p<0.05).

C-reactive protein (CRP) is a glycopretin that is produced by the liver and is related to inflammatory proteins in the acute phase. Under the influence of anti-inflammatory cytokines such as IL-1, TNF, IL-6, the production of CRP increases after 6-8 hours, and the level of content in the blood increases 10-100 times within 24-48 hours after the onset of inflammation. CRP is involved in the activation of complement.

Progressive increase in CRP is associated with the activity of the inflammatory process and the degree of tissue damage.

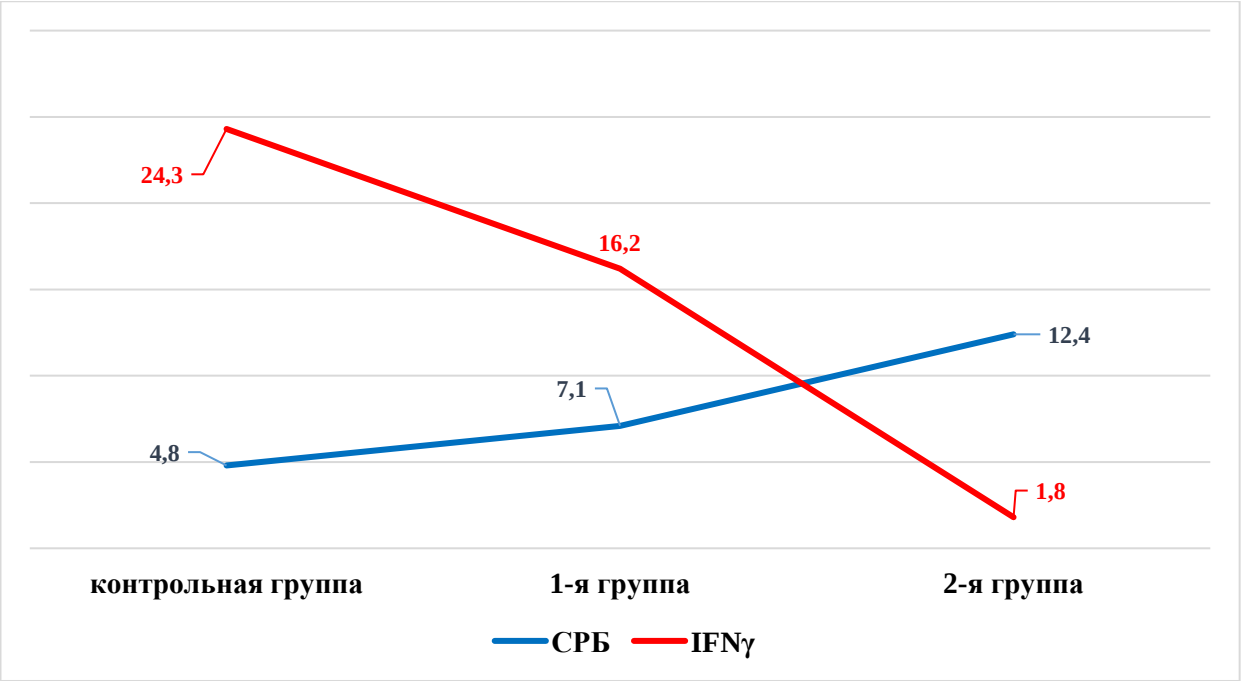

Fig. 4.3. Levels of CRP and IFNγ in examined women

7.1 ±1.2 ng/ml on average , which is quite higher than in the control group ($p<0.01$). At the same time, in patients of the second group, these indicators are 2.5 times higher than in the control group ($p<0.01$). These indicators indicate a large-scale chronic inflammatory focus, which occurs due to a reduced protective reaction. When infectious processes become chronic, the body stops providing adequate protection, even if the immune status is at a high level.

An analysis of the results of our studies on the level of IFN γ in the examined women showed that the average value in the control group was 24.3 ±1.4 pg/ml. In HIV-infected women, this indicator was lower than in the control group, and in the group not receiving ART, it was almost twice as low ($p<0.01$). (Fig. 4.4). One of the characteristic signs of CVD of the pelvic organs is a violation of the formation of IFN γ, which is involved in the regulation of homeostasis in the neuro-immunoendocrine link.

The interferon system is the main component of the body's protective ability, controlling the distribution and inclusion of immune cells in the process. During the reaction, interferon performs the task of short-range mediators of interaction between cells. I NF regulates the quality of the protective response of antigens, influencing the activation of MRS I and II antigens , as well as carcinoembryonic and atypical cell

antigens. IFN performs an identification function in the reaction of removing atypical "own" and foreign cells, being the main stimulator of cellular and phagocytic processes of protective properties. IFN - y is the main element of B-lymphocyte distribution.

The pathological effect of HIV infection is based on the disruption of the immune system by dysfunction of the interferon system. HIV infection has been classified into 3 stages :

1) HIV seroconversion, clinical manifestations are absent, but antibodies to HIV infection are found in the blood.

2) It consists of large-scale damage to the lymph nodes with subsequent disruption of their function.

3) Transition to AIDS with all clinical manifestations.

Disturbances in the IFN system are observed at all stages with more or less severity. HIV infection has all the properties of interferon, since it has the order of RNA 3- LTR to the beginning of the SP -6 paired helix, which has 80 nucleotides (40 pairs) in its composition. Being similar to IFN , HIV infection is also subject to standard antiviral principles - dsRNA-dependent 2', 5'-oligo (A) synthetase and protein kinase, triggers for activation of the formation of protein eiF 2. IFN-γ cannot completely suppress the division of the immunodeficiency virus, but only reduces its ability to divide by 70%, since retroviruses in this aspect differ from classic lytic viruses. All aspects of this phenomenon have not yet been studied, which provides motivation for further studies of IFN inhibitors at least at the 1st stage of the human immunodeficiency virus. Thus, the conducted studies on the parameters of cellular and innate immunity in the inflammatory process of the genital organs in HIV-infected women with and without ART showed that the level of natural killer cells is accompanied by reduced activity, which corresponds to the chronicity of the process. However, with a long-term course of the disease, a pronounced deficit in killer activity is observed, which is apparently associated with an increase in their local significance. The phagocytic process, being the central object of the body's defense, plays a key role in the inflammatory processes in the body. Low expression of

phagocytosis was found in all subjects, in particular in individuals of the 2nd group, who have reduced indicators of killer activity with a combination of reduced phagocytic reaction. The virus suppresses the immune reactions of the body, leading to a reduced number of cells in this group. Although the humoral elements of natural immunity, the C3 component of complement, as well as the level of IFN γ, have shown their inconsistency in the long-term course of the disease. It is noteworthy that the level of CRP did not depend on the duration of the disease and was significantly elevated in both women in group 1 and in group 2.

CHARACTERISTICS OF ADAPTIVE IMMUNITY INDICATORS IN THE EXAMINED WOMEN

Adaptive immunity or immunity acquired during life are factors that destroy foreign and microbes that have the ability to cause pathologies that were previously detected in the body. This response consists of a number of complexes localized in all parts of the body. Like innate immunity, acquired immunity is divided into cellular (T-lymphocytes) and humoral (antibodies produced by B-lymphocytes).

It was proven that the quantitative composition of leukocytes in the presence of HIV was significantly lower than normal values and was equal to 5.3 ± 0.15 mm ^{3} and 4.0 ± 0.3 mm ^{3} (P <0.01) (Table 4.2). The quantitative composition of lymphocytes was also lower than optimal values, but lower values were determined in the 2nd group (p> 0.01). It is worth emphasizing the decrease in the number of lymphocytes, which are noted for CD3. These indicators were also higher in the 2nd group, which are patients with HIV infection (Table 4.2.)

Table 4.2.

Absolute indicators of T-cell immunity in the examined subjects HIV patients with VZG, (M± m)

Indicator	Control group (n=30)	First group (n =99)	Second group (n =16)
Leukocytes,	6.3± 0.18	5.4 ± 0.16 *	4.1±0.31 *
Lymphocytes,	1.95 ± 0.06	1.22 ± 0.037*	0.8 ± 0.029*
CD 3+	1.04 ± 0.04	0.53 ± 0.032*	0.29 ± 0.012*
CD 4+	0.65 ± 0.03	0.25 ± 0.014*	0.12 ± 0.009*
CD8+	0.42 ± 0.02	0.21 ± 0.013*	0.108 ± 0.008*

*Note: *- values are reliable in relation to the control group (P<0.01-0.001)*

The 1st group averaged 0.53 ± 0.032 mm3 · which is almost 2 times lower than that of women in the control group (P < 0.001), and in women in the 2nd group - 0.29 ± 0.012 ^{mm3} , which is 2 times lower than that of women in the 1st group (P <

0.001).

There is a predominant decrease in the number of CD4+ cells responsible for the formation of T-helpers compared to healthy individuals. This type of cells is a target for HIV infection, and due to the symbiosis of 2 virulent viruses, the decrease in CD4+ cells is significantly enhanced. Due to the use of ART, an optimal value of CD4+ T-lymphocytes (26-32%) was noted, it was noted in 53%, while in the second group the number of such indicators was 5%.

The average decrease in the number of CD4+ T-lymphocytes (20-27%) was observed in 30% of subjects in the 1st group and in 70% of subjects in the 2nd group, which corresponds to the condition for this stage of HIV in subjects. Low rates of CD4+ T-lymphocytes (14-19%) were observed in 7% of subjects in the first group and in 18% of women in the second group. Dangerously low rates of CD4+ T-lymphocyte concentration (less than 14%) were observed only in 1.5% of women in the first group and in 8% of patients in the second group. It is worth noting the development of resistance to antiviral drugs in individuals in the 1st group with a low content of CD4+ T-lymphocytes, which prompted a change in the treatment method. A noticeable decrease in the number of CD8+ lymphocytes was revealed in the group of individuals who refused to take ART. Perhaps this is due to the suppression of each other by the functions of the viruses, or the inability of HIV to interact with CD8+ CD8 (Figure 4.4).

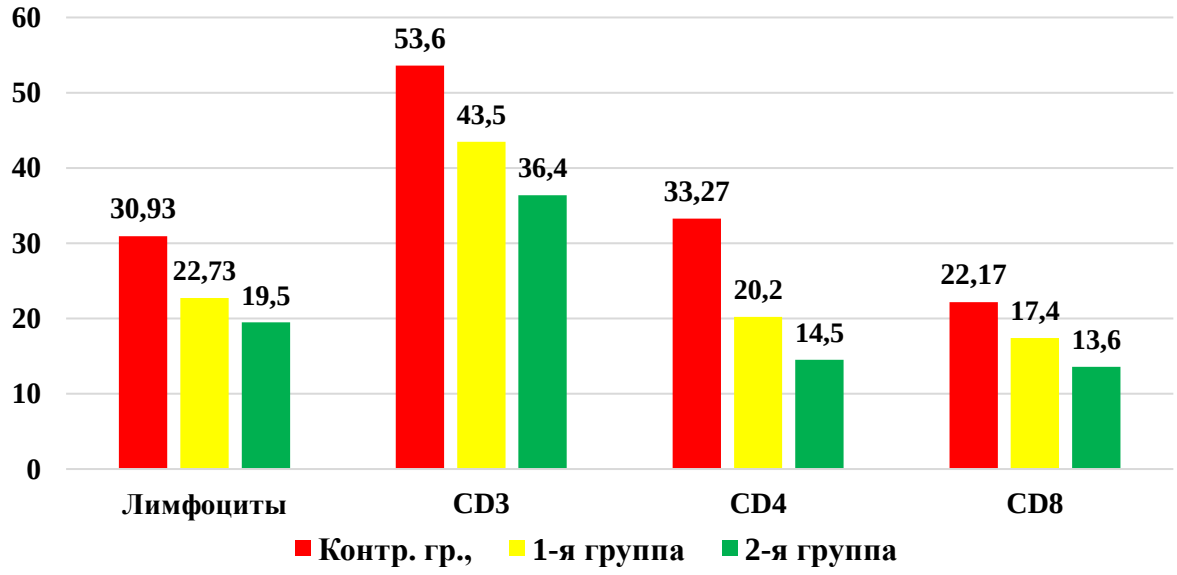

Fig. 4.4. Level of subpopulation composition of T-lymphocytes (CD4+ and CD8+ **) in the examined female subjects.**

For determining and predicting the progress of the disease, the immunoregulatory index (CD4+/CD8+) plays a high role. In our studies, these values are highly declining in relation to the control group data (P <0.01) (Fig. 4.5).

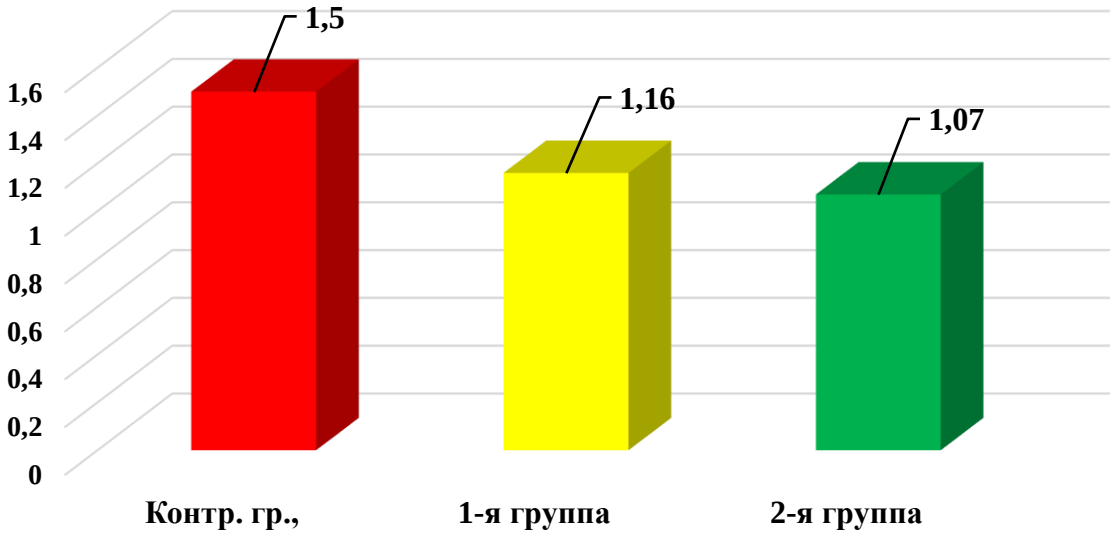

Fig. 4.5. Level of immunoregulatory index (IRI) in examined women

There is a concept that progressive decrease in the immunoregulatory index CD 4/ CD 8 correlates with the progression of HIV infection. To determine the expression values of lymphocytes in the peripheral parts of blood vessels corresponding to females with human immunodeficiency virus and with genital inflammatory processes, a comparative diagnosis of the activation of a number of markers on the lymphocyte membrane was carried out in women without HIV, patients with ART and without ART. The study assessed the features of the expression of early lymphocyte activation markers - CD 25 molecules, markers of the middle stages of activation - CD 71 molecules. In addition, the readiness of cells for apoptosis was assessed based on the determination of the expression level of CD 95

Таблица 4.3.

Особенности фенотипа периферических лимфоцитов с маркером активации у обследованных женщин, (M±m)

Обследуемые группы	CD25+, %	CD71+, %	CD95+, %
Контр. группа, n= 30	21,6 ± 0,9	23,2 ± 1,0	24,5 ± 1,0
1-я группа, n=99	18,5 ± 1,1*	21,07 ± 0,6	26,3 ± 0,9
2-я группа, n=16	14,9 ± 1,0*	19,2 ± 0,8*	28,6 ± 0,7*

*Примечание: * Значения достоверны по отношению к контрольной группе (P<0,05 - 0,001)*

molecules. The data obtained in the course of our study are presented in Table 4.3.

Changes in T-lymphocytes in women with HIV infection are manifested by a decrease in proliferation and cloning and a violation of the differentiation of CD 4+ and CD 8+ subpopulations. All these disorders are due to the loss of the ability to produce IL-2 [76; p . 56]. As can be seen from the data presented in Tables 4.3, the level of lymphocytes with the IL-2 receptor - CD 25+ cells - is significantly reduced in patients, with the minimum value recorded in women of group 2 (P < 0.001). The results obtained indicate that in the peripheral blood of women with HIV infection, both group 1 and group 2, the content of lymphocytes expressing CD 25 molecules on their surface was significantly reduced.

T-regulatory cells, which are lymphocytes with markers of rapid activation and the presence of a receptor for IL-2-C D 25+ cells, participate in maintaining

immunotolerance [125; pp. 2092-2098]. When their activity is disrupted, pathological processes occur, and as a result, research in recent decades has been aimed at studying the method for determining and changing their activity, as well as their numbers [66; pp. 102-103].

The interaction of mononuclear cells of HIV-infected patients with immune aggregates containing HIV antigens leads to a decrease in the relative number of double-positive CD71+ cells, activation markers of the middle stage. In our study, the level of CD 71+ cells in patients of the 1st group was 21.07±0.6%, in the 2nd group - 19.2±0.8% compared to the control group had an insignificant difference - 23.2±1.0%. At present, the main idea explaining the causes of activation of adaptive immunity cells in HIV infection is the concept based on the entry into the blood of microbial products from the genitourinary tract damaged by infection.

Apoptosis is one of the main mechanisms for preserving and maintaining the total number of cells in the body. This process occupies one of the leading functions of the immune system, regulating the number of cells. It is as a result of this mechanism that the process of expansion of activated cells is inhibited, as a result of which the development of inflammatory and autoimmune reactions stops. Activation apoptosis occurs against the background of a violation of activation signals and as a result of expression, and then the addition of specialized receptors for the induction of apoptosis. Immune mechanisms in this process implement and regulate the programmed course of cell death. Also, the process of apoptosis controls the activity of immunocompetent cells to antigen stimuli, determining the duration and prognosis of the immune response, forming immunological tolerance. Analysis of these cells indicates that the frequency of CD -95 expression on them in women of the first group does not exceed (26.3-27.1% compared to the control group, where this indicator varies within 24.1-25.2%) and there is a tendency to increase in women of the second group (28.4-29.2%).

Based on the obtained results, we derived the lymphocyte activation index from the ratio of the number of early activation lymphocytes (CD 25+) and late

activation stages (CD 95+), which is shown in Figure 4.6. As can be seen from the figure, the IAL in women of the control group was 0.88 conventional units, while in women of the 1st group this value was lower and was 0.7 conventional units, and in women of the 2nd group - 0.5 conventional units.

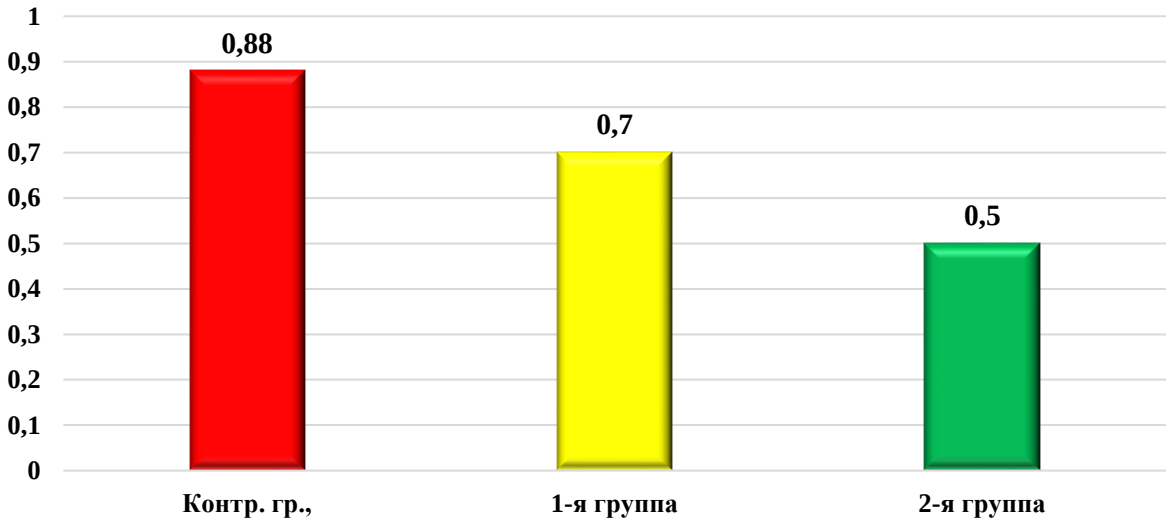

Fig. 4.6. Ratio of activation lymphocytes - Lymphocyte activation index (LAI), conventional units

Therefore, IAL can be used as a prognostic criterion for immunosuppression in HIV-infected women with inflammatory diseases of the genitals, both receiving and not receiving ART. And among women receiving ART, this indicator can be used to judge the adequacy of the dose and the selected ART regimen.

Таблица 4.4.

Показатели значений гуморального звена иммунитета у обследованных женщин, (M±m)

Иммунологические показатели	Контрольная группа (n=30)	Первая группа (n=99)	Вторая группа (n=16)
CD20+, %	25,9±1,0	29,7± 1,1*	34,5 ± 1,2*
IgG, г/л	9,3±1,3	13,8± 1,6*	16,2±1,9*^
IgA, г/л	1,6±0,1	1,97±0,2*	2,51±0,3*^
IgM, г/л	1,29± 0,13	1,6± 0,17*	1,83 ±0,2*^
ЦИК, ус.ед.	34,8± 1,5	69,5± 2,2*	79,2± 2,5*^

*Примечание: *Значение достоверно относительно контрольной группы*

^Значения достоверны относительно 1-й группы (P<0,05 -0,001)

In addition to the disorganization of cellular immunity, women with HIV infection and inflammatory diseases of the genital organs also have disorders in the humoral link. Along with dysregulation of the T-system, an increase in the total pool of B-lymphocytes (CD20+) was noted, which are key receptors for modulating the passage of a signal during antigen stimulation. Frequent exacerbation of the chronic process is accompanied by an increase in CD 20+ lymphocytes. It was found that the level of B-lymphocytes was significantly increased both in women of the 2nd group (34.5 ± 1.2% versus 25.9 ± 1.2% in the control, $P < 0.01$) and in women of the 1st group (29.7 ± 1.1%, $P < 0.05$) (Fig. 4.7.)

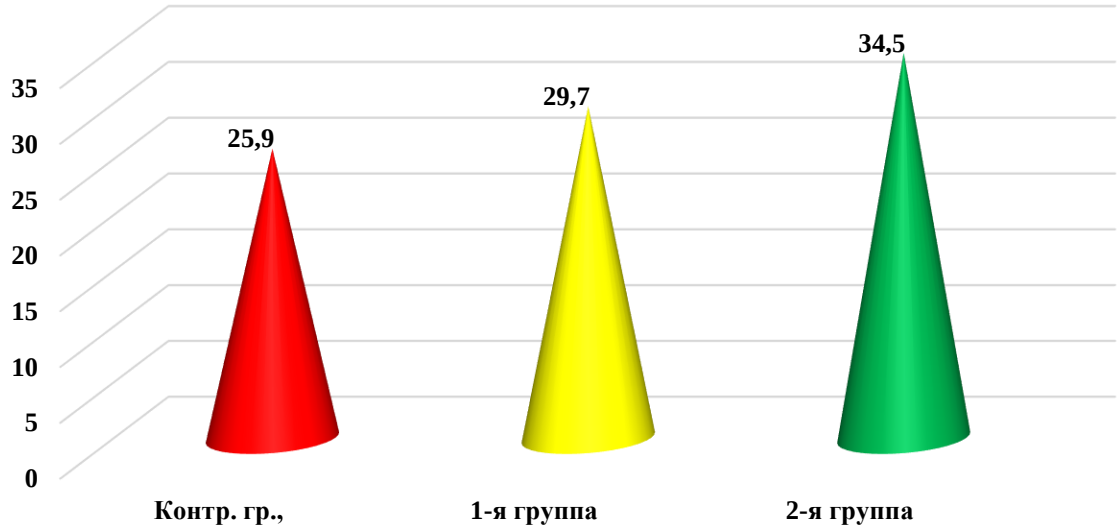

Fig. 4.7. Level of B-lymphocytes (CD 20+) in examined women, %

When the brain receives a signal about the entry of an antigen into the body, the process of transformation of B-lymphocytes into plasma cells is launched, which begin to synthesize antibodies. These data indicate that in people with human immunodeficiency virus, all inflammatory processes of the genitals occur with a feedback between the amount of immunoglobulins in the blood serum and the number of migrating producer cells. It is worth noting that the growth of globulin is directly proportional to the development of inflammation.

As a result, the virus in symbiosis with inflammation has an effect on the expression of B-lymphocytes, and with chronicization of the process, the process of formation of immunoglobulins increases, in particular, IgG , 95% of which is non-

specific. It has been proven that IgG is formed in women of the control group from 8.5 to 14.2 g / l with an average content of 9.3 ± 1.3 g / l.

In women of the 1st group, the IgG concentration was significantly increased (13.8 ± 1.6 g/l) (P < 0.005), (Fig. 4.10), and in patients of the 2nd group it was 1.7 times higher than in the control group - 16.2 ± 1.9 g/l with fluctuations from 12.8 to 18.5 g/l (P < 0.01) (Fig. 4.8).

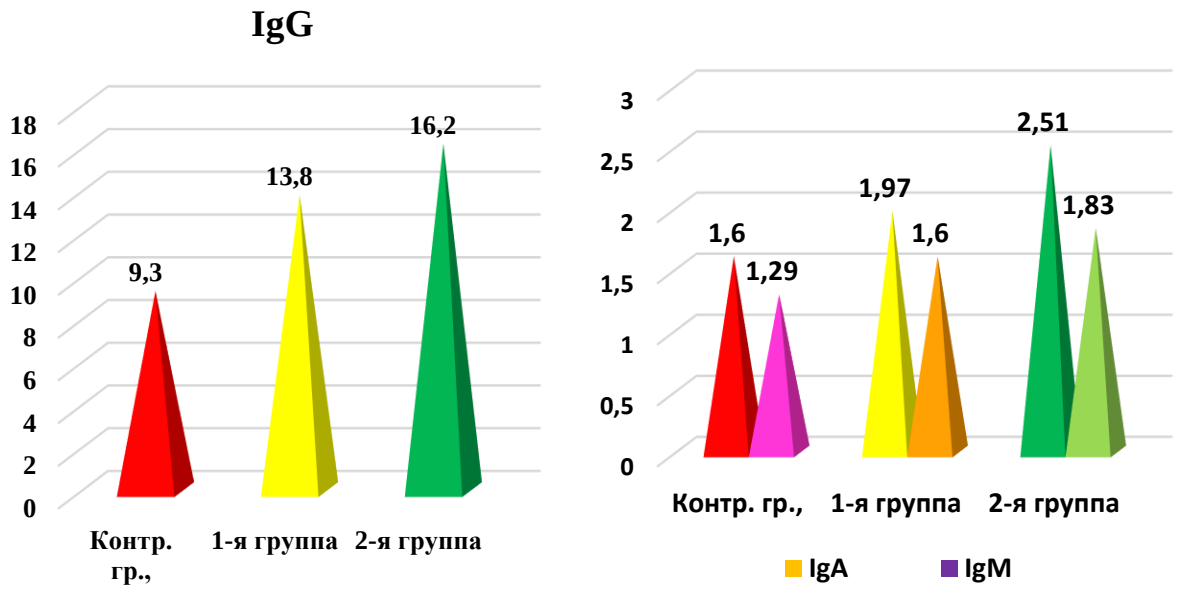

Fig. 4.8. Immunoglobulin levels in examined women, g/l

IgA level in the blood serum of women in the control group ranged from 1.0 to 1.8 g/l, which averaged 1.6 ± 0.1 g/l. In the peripheral blood serum of women in group 1, the IgA concentration was significantly increased - 1.97 ± 0.2 g/l (P < 0.05), and in patients in group 2, a more pronounced increase was observed, by 1.6 times, which averaged 2.51 ± 0.3 g/l (P < 0.01).

The study of the IgM level showed that in the group of women of the 1st group its concentration was significantly increased, averaging 1.6 ± 0.17 g/l (P<0.05). And in women of the 2nd group there was a reliable increase in IgM by 1.4 times (P<0.05).

According to a number of authors, the main role in the development of the inflammatory process in women with HIV infection is played by the inability of the woman's immune system to localize the source of possible infectious aggression and

eliminate the pathogen. Consequently, the body's resistance to infections will be largely determined by the functional state of B-lymphocytes. Pronounced disorders of B-cell immunity are associated with the inflammatory process of the genital organs and its clinical manifestation.

In women with HIV infection, a reliable increase in the CIC titer was revealed in VZG (Fig. 4.9). The CIC level in women in the control group averaged 34.8 ± 1.5 conventional units. Inflammatory processes contribute to the accumulation of circulating immune complexes, which in turn aggravates this process. Thus, in women in group 1, the CIC level averaged 69.5 ± 2.2 conventional units, which is almost 2 times higher than the values in the control group ($P < 0.001$). In women in group 2, the CIC level was even higher - 79.2 ± 2.5 conventional units ($P < 0.001$).

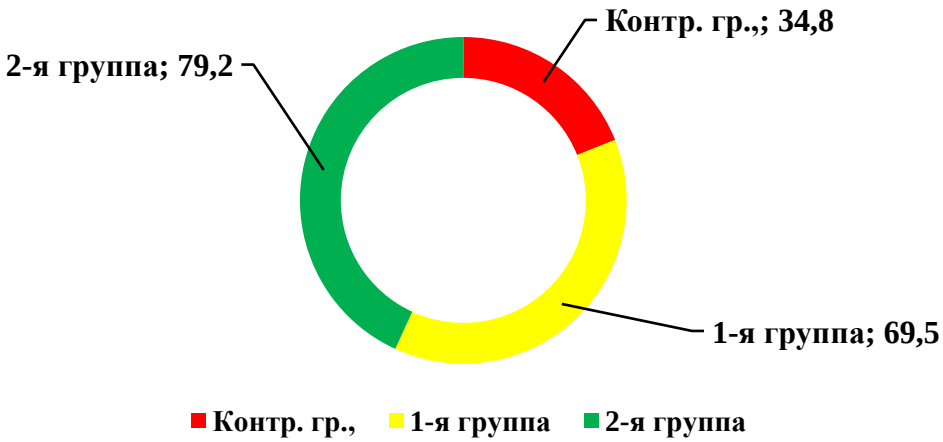

Fig.4.9. The level of CIC in the examined women, conventional units.

These values indicate a defect in phagocytic cells due to the long presence of the antigen in the body, which is evidenced by the high content of infection in the vagina.

It has been confirmed that inhibition of the phagocytic system component and imbalance of the amount of immunoglobulins in the blood serum have an effect on the imbalance of the complement system, but the main factors are the expression of antibody synthesis, especially IgG . The property of B-lymphocytes to change the formation of a group of antibodies is based on intercellular connections with the

calculation of various cytokines. The negative effect of pathogens on lymphocytes, leading to a decrease in their number, indicates the suppression of the properties of cellular immunity.

Thus, the examined women showed changes in the immune system, classified as secondary immune deficiency (SID). The degree of change in the parameters of innate and adaptive immunity depends on the duration of the inflammatory process. SID reveals polygenic defects: an increase in B-lymphocytes, increased T-suppressor activity, insufficiency of T-helper function, and a violation of T-B-cell interaction.

Thus, in women with HIV infection and inflammatory diseases of the genital organs, there is a change in the population composition of mononuclear cells in the peripheral blood. These changes are most likely due to the peculiarities of the pathogenetic mechanisms of HIV infection development.

Consequently, changes in the adaptive and innate immune system, both enhancement and deficiency in HIV-infected women, are classified as secondary immunological deficiency.

. Cytokine status indicators in examined HIV-infected women with VZG

C D 4+ lymphocytes, which act as helpers, primarily participate in the formation of antibody-producing plasma cells from cells, and secondly, they participate in the synthesis of cytotoxic T cells from C D 8+ lymphocyte cells. Among other things, they help macrophages maintain their hyposensitivity properties. All of the above functions of T lymphocytes arise against the background of their division into two populations as Th 1 and Th 2, which act as helpers as a result of their formation of IL.

Initially, two types of cells were noted between CD4+ T cells depending on the formation of certain cytokines Th 1 and Th 2. Th 1- are responsible for cellular immunity, while Th 2 for humoral immunity. Th 1 secretes Interleukin-1 β, Interleukin-2, Interferon-γ and α - Tumor necrosis factor. IFN - γ in large quantities leads to the expression of CD8+ T cells, which leads to the death of pathogenic cells. IFN - γ also inhibits the activity of Th -2 cells responsible for the work of Th 1 cells.

An increase in the production of Th 2, as well as a decrease in the production of Th 1 and IL -4, has been proven. The presence of IL -4 indicates an increased formation of Th 2-type cytokines. IL -4 and 8 also inhibit the expression of Th 1 cells. Th 1 cytokines are inflammation instigators, while Th 2 are inflammation inhibitors. HIV is characterized by the presence of a chronic inflammatory process. IL -4 plays a major role in the response to inflammation.

In our study, we observed a significant decrease in IL -4 activity in the observation groups - 34.18±1.0 in the 2nd group and 37.5±0.9 pg/ml in the 1st group compared to the control values - 79.48±49.71 pg/ml, $p < 0.05$.

In the processes of regulation of innate and adaptive immunity, one of the main types of cytokine is IL 8, the main function of which is to regulate the antigen-dependent immune response based on its participation in stimulating the proliferation and differentiation of immune cells, including T-lymphocytes. We can assume that an increase in the content of IL8 in the blood also affects the disruption of the proliferation and differentiation of immunocompetent cells in patients with HIV infection. This condition affects the development of drug resistance in the virus under conditions of constant replication of the virus and the presence of concomitant pathologies of lower genital tract infections.

Thus, in women under our observation and receiving ART, the IL -8 level was 33.3±2.1 pg/ml, and in patients who refused pathogenetic therapy - 35.45±1.78 pg/ml, compared with control values - 23.02±0.82 pg/ml, ($p \leq 0.0\ 0\ 1$).

Research into the functions of Th17 has shown that they produce IL 17, which has the functions of a strong proinflammatory cytokine, which performs an important task in protecting the body from microorganisms, fungi and autoimmune processes.

When assessing the average values of serum interleukin-17 in the groups subject to study (Tables 4, 5), a noticeable increase was noted, compared with the control group, in the amount of serum interleukin-17 in individuals with human immunodeficiency virus with severe immunodepression due to a decrease in CD4 + lymphocytes below 200 μl-1, who refused to undergo ART, and this indicator was equal to 111.3 ± 11.5. pg / ml. This proves an increase in the concentration of interleukin-17 in patients with severe immunosuppression who did not undergo ART. ART significantly inhibits virus division, which is proven by the presence of a decrease in the viral load and confirmed by us - the level of IL -17 in the 1st group of patients was higher than the control values, but reliably lower in comparison with the 2nd group - 89.4 ± 9.8 pg / ml ($p \leq 0.0\ 0\ 1$) .

Таблица 4.5.

Цитокиновый статус обследованных женщин

Показатель	Первая группа (n=99)	Вторая группа (n=16)	Контрольная группа (n=30)	p
IL-4 пг/мл	37,5±0,9*	34,18±1,0*	79,48±49,71	p<0,05 *
IL-8, пг/мл	33,3±2,1*	35,45±1,78*	23,02±0,82	p≤0,001*
IL-17/A, пг/мл	89,4±9,8*^	111,25±11,5*	29,2±1,98	p≤0,001*

*Примечание: *Значения достоверны по отношению к контрольной группе*

^Значения достоверны по отношению ко 2-й группе (p<0,05 - 0,001)

During HIV, a significant decrease in Th17 is recorded, also in lymphoid tissues that have mucous membranes (gastrointestinal tract, respiratory tract, excretory tract). It is in this localization that Th 17 performs a significant function of regulating local microflora and limits its movement through the bloodstream. In this mechanism, the ability of interleukin 17 to stimulate the formation of enterocytes is important, which is a restraining factor for migration. It follows that during HIV infection, which suppresses the formation of Th -17, leads to the destruction of

mucous membranes and leads to the migration of microflora through the bloodstream.

As a result, due to migration, there is a massive activation of defense mechanisms, which leads to a huge amount of HIV replication, which inevitably leads to a decrease in the concentration of CD4 + lymphocytes and further development of HIV infection. Against this background, opportunistic flora is exacerbated, leading to inflammation, and these are, in particular, bacteria and fungi, during which Th 17 performs the main protective function, which was identified in the patients we studied, caused by non-specific flora, with cervicitis and candidiasis and colpitis. Along with this, the production of Th 17 cytokines increases, namely interleukin-17, already on a scale of blood serum, and not just mucous membranes. This phenomenon was noted in the subjects of the first and second groups. With significant indicators of immunodepression and exacerbation of opportunistic microflora, the production of IL -17 increases significantly. ARVT has the property of suppressing the division of the virus, at the same time increasing the concentration of T-helpers, including Th 17, which rehabilitates the condition of the mucous membranes. Due to these actions, there is a reduction in the migration of the flora of the mucous membranes, which leads to the extinction of protective activity and is manifested in a decrease in proinflammatory cytokines (IL -17). High levels of interleukin-17 in the serum of patients with the immunodeficiency virus indicate a general activation of the protective system in patients with severely suppressed immunity. Due to the control of the production of various cytokines by means of ARVT therapy, it can cause positive results in the treatment of HIV infection at late stages and in the formation of AIDS-associated lesions.

The study showed inhibition of the natural and cellular immune response due to high levels of cytokines such as IL 8, IL 17, and suppression of IL 4 production in the blood serum. In theory, this is a normal physiological response to a pathogen, but a low phagocytic response entails an imbalance of cytokines and their inactivation. This picture is observed in chronic inflammatory diseases of the genitals. High levels of IL 8 and IL 17 A in the blood serum of patients with the immunodeficiency virus

are a sign of general activation of the immune system due to a strong decrease in the number of CD4 + lymphocytes in the last stages of HIV infection. There is a possibility that ART therapy with control of the content of specific cytokines in the blood can improve the results of this therapy at different stages of HIV infection, as well as in the development of AIDS-associated lesions and concomitant inflammatory diseases of the genitals.

§ 4.4. Algorithm for the management of HIV-infected women with VZG

The method of introduction of HIV-positive females with inflammatory diseases of the genitals provided by us includes: unconditional visit to the doctor at the time of registration in the register, full clinical and laboratory examination in order to confirm or identify the cause and location of the inflammatory diseases of the genitals. Primary consultation includes a detailed review of ART schemes, in case of earlier refusal to conduct ART, informing on the issues of risks for somatic and when planning reproductive tasks - obstetric risks in the future with the aim of immediate initiation of ART. The next stage is an immunological examination, including the definition of CD 25 +-, CD 95+-, IL 17 A.

It is necessary to calculate the lymphocyte activation index - CD 25+/ CD 95+, if this ratio is less than 0.7 conventional units and the IL 17 A level is more than 3 times higher than the standard values in women who received ART, then they need to undergo preventive therapy even in the absence of signs of VZG activity. For women who have not received ART, it is necessary to immediately start ART. If this indicator is less than 0.5 conventional units, for women who received ART - a revision of the regimens and / or doses of ART and treatment by a gynecologist, and for women who have not received ART - immediately and forcibly start ART and treatment for VZG with control after 1 and 3 months (Fig. 4.9).

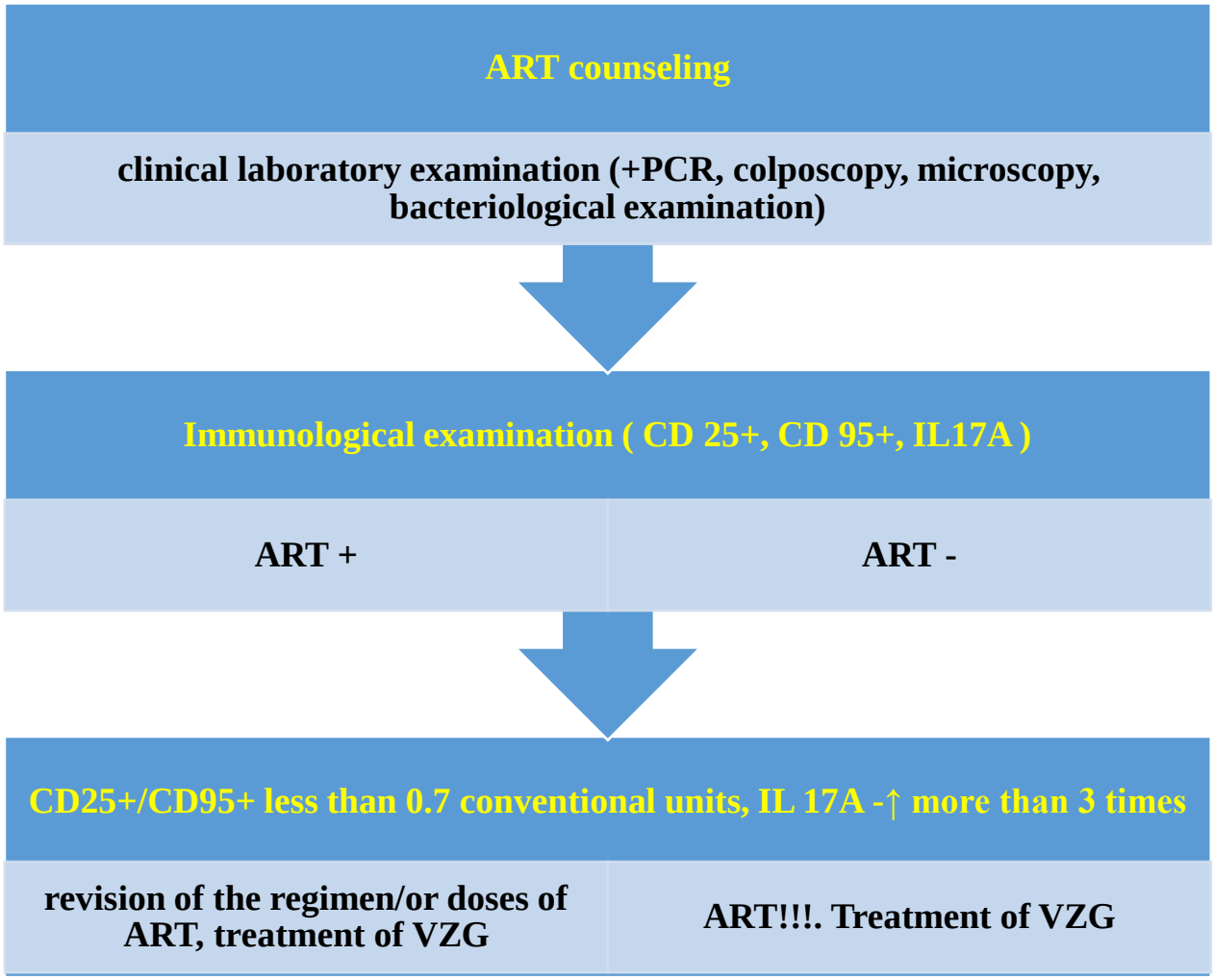

Figure 4.9. Algorithm for the management of HIV-positive women with VZG

Based on this, using these clinical and laboratory indicators for diagnosing immunosuppressive processes in HIV-infected women with VZG, an individual treatment strategy was determined for each patient. When considering anamnestic risk factors and the results of clinical and laboratory indicators and symptoms, it is possible to carry out timely diagnostics and, if necessary, carry out therapy for this pathology. This makes it possible to establish the degree of risk and progression of immunosuppressive processes in HIV-infected women who have consulted a gynecologist about VZG.

CONCLUSION

The scale of the spread of HIV infection and AIDS worldwide are important aspects in public health. However, significant advances in the study of the human immunodeficiency virus, its molecular genetic bases and the introduction of antiretroviral therapy into routine clinical use, HIV-associated infection, loss of ability to work, at the moment, mortality remains at a high level. The incidence of HIV infection is most often found among women in the reproductive period of life. In women with HIV infection, changes in the clinical manifestations of inflammatory diseases of the pelvic organs and reproductive organs are noted in current conditions. Weakly expressed, inactive forms of the disease prevail, having an exacerbation character, which are noted with an increase in the frequency of polymicrobial associations, in which the majority is opportunistic flora with its resistance to antibiotics. Acute inflammatory diseases of the pelvic organs are a set of symptoms that occur as separate diseases in the form of inflammation of the endometrium or fallopian tubes, pyosalpinx, tubo-ovarian abscess and peritonitis of the pelvic region or another possible combination. And this becomes a reason for referring treatment to a gynecological hospital, which accounts for 30-50% of cases. However, the distinctive factors of the course of inflammation processes, the incidence and quality of complications caused by the human immunodeficiency virus, and the use of antiretroviral therapy are still poorly understood. In this situation, the main task is to restore the functionality of the reproductive system of women with the subsequent birth of children without congenital HIV infection, as well as to protect the partner from the transmission of this infection. Such goals are achievable by following the rules for the treatment of HIV-infected women with the appropriate therapy, as well as controlled conception of a child with further observation of the entire period of pregnancy. But at present there is no 100% evidence of the impact of ART on sexual function of both men and women, which in turn entails ignorance of the impact of this therapy on the chances of pregnancy. And of course, the percentage of detection

of pathologies of the reproductive system with an inflammatory process compared with the characteristic groups obtained from data on the population.

In connection with the above, we conducted a thorough processing of clinical data of female individuals with HIV infection. A total of 315 individuals aged 15 to 41 years were examined. Clinical and laboratory data of 200 patients were analyzed retrospectively for 2018-2019 (comparison group), 115 individuals were under observation during 2020 (main group). The control group consisted of 30 women without HIV infection. The work was carried out during 2019-2020 at the AIDS Center outpatient clinic, the gynecology department of the Regional Perinatal Center, and the Bukhara Reproductive Center. A total of 315 patients aged 15 to 41 years were examined. Clinical and laboratory data of 200 patients were analyzed retrospectively for 2018-2019 (comparison group), 115 patients were monitored during 2020 (main group)

In the process of analysis, in order to confirm the data, we studied the conclusions of a number of women's consultations, in particular, personal cards of pregnant women and women who have recently gone through the birth process (form 111 / y .), dispensary cards (form 025 / y). Women were provided with assistance on the basis of an active order of the Ministry of Health of the Republic of Uzbekistan (to the decree of the President of the Republic of Uzbekistan starting from 11/8/2019 No. PP-4513). The study of women with immunodeficiency viruses and the introduction of HIV-positive females was also carried out in accordance with regulatory documents: Resolution of the President of the Republic of Uzbekistan dated 06/22/2018 No. PP-3800 "On additional measures to counter the spread of the disease caused by the human immunodeficiency virus and the prevention of nosocomial infections. Persons of the main study group were provided with ART based on the instructions added since 2018 to the state program to counter the spread of HIV infection in the Republic of Uzbekistan for 2018 (Appendix to the Resolution of the President of the Republic of Uzbekistan dated 01/25/2018 N PP-3493).

The average age of patients in the comparison group was 38.6±0.67 years , in the main group 35.1±0.65, in the control group 34.93±1.50 years, $p \leq 0.05$.

The information obtained during the study confirms the presence of such a fact as an increased registration of the human immunodeficiency virus in individuals of active and at the same time reproductive age. In our study, as in other previous analyses, the fact of an increase in the average age of patients with the human immunodeficiency virus with infection in adolescence was confirmed, which indicates an extension of the average life expectancy with this infection against the background of the conducted ART therapy. We conducted a survey of the surrounding life factors studied in both groups. The percentage of women with secondary and secondary specialized education was significantly higher in the examined women of both groups compared to women with higher education. When analyzing professional affiliation, we took into account the possible impact on the occurrence and development of the underlying disease depending on the conditions and factors of labor activity. The overwhelming majority of HIV-infected women are housewives or temporarily unemployed. It should be noted that the majority of HIV-infected women were not married (58.5% in the comparison and main groups), and in the groups with female subjects not receiving ART treatment, the number of unmarried women significantly exceeded the number of patients undergoing antiretroviral therapy, 35 (41.5 ±%) and 18 (24.5 ±%), ($p < 0.05$), taking into account the fact that divorce occurred in 10 (13.4 ±%) and 32 (37.5 ±%), ($p < 0.01$) in the comparison group after diagnosis of HIV infection. Of the bad habits in the comparison group, 20% noted smoking and 20% - regular alcohol consumption, in the main group - 25.2 and 22.6%, respectively. The spouses of the examined women in the comparison group were not infected in 64.5% of cases, in the main group - in 54.5% of cases.

The route of infection in 40% of cases in the comparison group and in 43.5% is sexual, it should be noted the high percentage of unknown route of infection in 46.5% and 40%, respectively, 27 (13.5%) patients of the comparison group, as well as 19 (16%) female individuals from the main group, who were infected by injection, which is logical when using drugs, patients indicated having experience of taking drugs in the past, but did not consider themselves drug addicts, referring to a single or

accidental intake of these drugs during adolescence. The duration of HIV infection among those examined retrospectively was: 1 year in 10.5% of those examined, 2 years - 10%, 3 years 17% and more than 3 years - 62.5%; In those examined prospectively, the disease duration for 1 year was 10.4%, 2 years - 10.4%, 3 years - 16.5%, and more than 3 years - 62.6%. Most of the subjects were infected in the last 2-3 years. Infection less than one year was noted in 16% of the subjects, and infection more than 10 years ago was 11% in the comparison group, and in the main group 18 and 12%. It is worth noting that in most patients the time of establishment of the immunoblot was less than 12 months, which again confirms the increasing role of sexual infection.

We would like to focus on the presence of bad habits that worsen metabolic processes in the liver and create conditions for worsening the inflammatory and dysplastic process of the cervix in the context of HIV infection - alcohol abuse was noted by 20% of patients from the comparison group and 23% of patients from the main group.

We noted a lower frequency of general somatic pathology in the examined patients, possibly due to the rare frequency of seeking medical attention due to the presence of the underlying pathology.

The following results were obtained from the analysis of reproductive function. One pregnancy in the anamnesis was present in 9.5% of patients from the comparison group, in 9.6% of the main group, two pregnancies were present in 63% and 63.5% of the examined women, more than three pregnancies were present in 23% and 22% of the women. On average, more than 66% of the examined women in both groups gave birth two or more times.

Antiretroviral therapy is received by 85.5% of patients in the comparison group and 86% in the main group. The duration of etiopathogenetic therapy in the comparison group is as follows: 1 year - 21% of patients, 2 years - 9%, 3 years - 20% and more than three years - 50%, in the main group - for 1-2 years received 10.5% of patients, for 3 years - 16.6%, more than three years - 62.4%. Among the examined patients, a low incidence of viral hepatitis was noted, which is most likely due to the

high frequency of undiagnosed cases - the incidence of viral hepatitis B was 6% of cases in the comparison group and 5% of cases in the main group, viral hepatitis C was 2 times less common . As a complication of the underlying disease, our patients noted "chronic" diarrhea in 21% of cases from the comparison group, 22.6% from the main group, relapses of upper respiratory tract infections were noted by 23% and 23.5%, respectively.

The reproductive history of the vast majority of women was not optimal, due to medical terminations of pregnancy or accidental terminations of pregnancy by miscarriage. It is worth noting that the number of intentional terminations of pregnancy in people with human immunodeficiency virus was significantly higher and amounted to more than 25%. Perhaps this value is associated with the low awareness of patients about contraception. In our study, we would like to note the fact that the number of early births occurs 7 times more often than in the control group, which indicates low health indicators in this group. It is inevitable that this provokes the development of vegetative dystonia. This proves the basis for considering these criteria as markers for the development of chronic VZG.

In the information, the number of births was significantly lower, while unexpected terminations of pregnancy were more common. In the presence of VZG, the postoperative periods of cesarean and abortions are much more difficult. It is worth noting that during the studies and detection of HIV carriage during pregnancy, after consultation, 22 women consciously refused to undergo ART (11%). In 63 women, which is 32%, HIV infection was detected in maternity hospitals, since these individuals were not recorded in the register of pregnant women in the antenatal clinic departments.

It is worth noting that women who underwent ART therapy before or during pregnancy with 100% frequency preferred to refuse breastfeeding.

In terms of the nature of the menstrual function, the overwhelming majority of those examined (83% of the comparison group and 82.6% of the main group) had a normal menstrual cycle. IUD carriers are 29% of those examined in the comparison group, 25.2% of those in the main group, compared to 36.7% in the control group;

COCs are used by 7.5%: 12.2%: 20%, respectively; barrier methods of contraception are used by 9%: 7.8%: 23.3%; injection methods are used by 4%: 3.5%: 6.7%, DHS in 8%: 7%: 10% of those examined, respectively. Proliferative processes of the uterus were extremely rare and were represented by uterine myoma, which was diagnosed in 2 patients (1%) from the comparison group and in 1 (0.9%) from the main group, endometriosis in 2% (n = 4) and in 1/7% (n = 2) of patients, respectively.

The factors of progress of VZG are the influence of pathogens, which gives grounds to be changes in the work and composition of tissues causing inflammatory processes. Various microbes act as triggers. It is worth considering the presence of pathogenic microflora without clinical manifestations, such microbes include chlamydia, localized in the cervical canal and on the endometrium. The driving factor remains that at present, both harmful and conditionally harmful microbes can be triggers of inflammatory responses. It has also been proven that HSV, CMV and HPV are factors in symbiosis with microbes of the cervical ducts and endometrium cause a decrease in the immune process and lead to chronic infectious diseases. Due to the combination of infections in VZG, a non-standard clinical development of the disease is based on the resulting combination of microorganisms, leading to complications of the immune response processes, which leads to frequent relapses. Leukocytosis in cervical discharge in the comparison group averaged 34.16±0.26, in the main group - 34.65±0.18 compared to the control - 14.1±0.1, $p \leq 0.001$. High pH values are noted in 70% of women (pH 6.5±0.5), growth (pH 5.5±0.5) in 30% of the comparison group; in 60% of the subjects (pH 6.5±0.5), growth (pH 5.5±0.5) in 42% of the main group.

More than 60% of both groups were diagnosed with colpitis, in 23% of cases bacterial vaginosis. The percentage of nonspecific colpitis prevailed - 21.5%, cervicitis and endocervicitis in 55% of cases in the comparison group, in the main group - cervicitis in 47%, chronic endometritis in 3.5% of cases, candidal colpitis in 13% of cases. According to the structure of the biocenosis in the comparison group with vaginitis, several variants of the state of the biocenosis were distinguished: absolute normocenosis - in 21%, vulvovaginal candidiasis in 25.6%, aerobic

dysbiosis in 8%, obligate anaerobic dysbiosis in 15.5%, aerobic-anaerobic dysbiosis in 9% and mixed dysbiosis in 21%. In 77 (38.5%) patients, Ureaplasma spp. was detected in an amount of more than 10*4 CFU/ml, which was considered as a possible etiologic factor of vaginitis; in 18 (9%) – HSV type 2. In women from the main group, absolute normocenosis was noted in 20%, vulvovaginal candidiasis in 27.8%, aerobic dysbiosis in 7.8%, obligate anaerobic dysbiosis in 18.2%, aerobic-anaerobic dysbiosis in 7.8% and mixed dysbiosis in 18.2%. In 29.5% of patients, Ureaplasma spp. was detected in an amount of more than 10*4 CFU/ml, in 9.5% – herpes simplex virus type 2.

The study did not record detection of such an infection as gonococcus or chlamydia, which are considered the main causes of VZG, which gives the right to be the conclusions of other scientific works, asserting the importance of opportunistic flora in the development of inflammation in the pelvis. Diagnosed in the studied women with VZG cerfictitis and vaginitis, which lead to a violation of the balance of flora, which entails a long-term preservation of opportunistic flora and long-term inflammation. The fact of the human papillomavirus in an amount of more than 10 * 3 cells is recorded in 65%, VGP is diagnosed in 60% of the studied, while the combined presence of the virus and bacteria was found in 82% of women. The presence of mixed pathogens explains the fact of the ineffectiveness of treatment and attempts to chronicize processes. The results of the microbial landscape can vary from many factors, including the choice of antibiotic therapy.

PCR testing of endocervical scrapings in the examined women revealed monoinfection in an average of 18% (36/18) of cases and mixed infection in 81.4% (36/18). These patients complained of heavy vaginal discharge (58.2% of the comparison group (n = 23) and 61% of the main group (n = 11)), unpleasant odor (25.5% and 31.4%), itching (10.9% and 14%), and burning (67.3% and 72%) in the vagina. Chlamydia trachomatis was detected in 24% of the comparison group, Mycoplasma hominis and M. genitalium – in 4.5 and 6.3%, respectively; Ureaplasma urealyticum, U. spp. and U. parvum – in 10.7, 51 and 28%, respectively; Herpes simplex virus – in 27% and Human papilloma virus 16 and 18 serotypes – in 22% of

women. In patients of the main group, we observed the following - Chlamydia trachomatis was detected in 19% of those examined in the comparison group, Mycoplasma hominis and M. genitalium – in 7 and 5.2%, respectively; Ureaplasma urealyticum, U. spp. and U. parvum – in 15, 48 and 23%, respectively; Herpes simplex virus – in 31% and Human papilloma virus 16 and 18 serotypes – in 22% of those examined.

The mobilized status of immune protection in the presence of inflammatory processes in the female genital organs, as well as reduced immunity, is a fact. The influence of cytokines on inflammatory processes has been proven, the quantitative and qualitative composition of which plays a major role in the characteristics of the course of the disease, and their imbalance is considered a dysfunction of the intermediate link of the immune response.

In the presence of an inflammatory process of the genital tract in females, the status of the cellular response plays a major role in the course, frequency and type of recurrence of this pathology.

To study the immunological parameters, a group of prospective female patients (n = 115) with an inflammatory process in the genital organs was divided into two subgroups: Group 1 included 99 women receiving ART (86%) and Group 2 included 16 women who did not receive ART (14%). The obtained data were compared with the values of immune parameters in 30 healthy women of reproductive age. The relative level of CD 16+ cells in women of Group 1 was lower than the values of the control group and averaged 12.6 ±1.4% versus 13.7 ±1.1% in the control ($p < 0.01$), while in women of Group 2 the level of killer activity was significantly reduced (9.7 ±1.1%) relative to the control group ($p < 0.05$) and 1.3 times lower than the values of Group 1 ($p < 0.001$). The same dynamics was observed in relation to the absolute values of CD 16+ cells ($p < 0.05$). A reduced level of these cells indicates the presence of an inactive inflammatory process associated with an excess of the infectious pathogen, and thus indicates the chronicity of the inflammatory process.

In the examined women, the level of phagocytic activity was reduced, and a more profound deficiency was observed in women who did not receive ART. It was

noted that patients with impaired phagocytic activity of neutrophils suffer from recurrent infections. The level of the C3 component of complement in HIV-infected women receiving ART was significantly increased, averaging 47.3 ±1.6 ng / ml, which is 1.4 times higher than the values in the control group, $p < 0.01$. The level of CRP in women of the 1st group averaged 7.1 ±1.0 ng / ml, which is significantly higher than in women of the control group ($p < 0.01$). And in women of the 2nd group - 2.5 times higher than the control values ($p < 0.01$). Such a level of CRP is characteristic of chronic inflammatory processes, which, apparently, reflects its generalized nature and, to a certain extent, some insufficiency of immune protection. Analysis of the results of our studies on the level of IFN γ in the examined women showed that the average value in the control group is 24.3 ±1.4 pg / ml. In HIV-infected women, this indicator was lower than the control, and in the group not receiving ART, almost twice ($p < 0.01$). Violation of the production of IFN γ, which plays an important role in maintaining homeostasis at the level of neuroimmunoendocrine interactions, is characteristic of chronic inflammatory diseases of the pelvic organs and genitals.

Adaptive immunity is the result of interaction of highly organized cells localized throughout the body. Like innate immunity, acquired immunity is divided into cellular (T-lymphocytes) and humoral (antibodies produced by B-lymphocytes). As a result, in patients with human immunodeficiency virus, the concentration of leukocytes is significantly reduced and is 5.5 ± 0.15 mm ^{3} and 4.1 ± 0.3 mm ^{3} ($p < 0.01$). The concentration of lymphocytes was also below normal, in particular in individuals belonging to the 2nd group ($p < 0.1$). A significant decrease in the indicators of lymphocytes, which are precursors of CD3 cells, was diagnosed, and this phenomenon is more pronounced in individuals of the 2nd group due to HIV infection. With a high chance ($p < 0.004$) a decrease in the concentration of CD4 + cells, in particular T-helpers, compared to healthy individuals. This type of cells is the primary target of HIV infection, which is exacerbated by the presence of 2 virulent viruses. During ART therapy, the optimal concentration of CD4+ T-lymphocytes (29-30%) was observed in 53% of patients, in the second group, these

figures were 5%. The average decrease in the concentration of CD4+ T-lymphocytes (20-25%) was observed in 29% of subjects in the first group and in 70% in the second group, which is normal for the current clinical period of the disease.

Low CD4+ T-lymphocyte levels (14-19%) were observed in 7% of subjects in the first group and in 18% of women in the second group. Dangerously low CD4+ T-lymphocyte concentration levels (less than 14%) were observed only in 1.5% of women in the first group and in 8% of patients in the second group. It is worth noting the development of resistance to antiviral drugs in individuals in the first group with low CD4+ T-lymphocyte levels, which prompted a change in the treatment method.

A significant decrease in the number of CD8+ lymphocytes was revealed in the group of people who refused to take ART. Perhaps this is due to the suppression of each other by the functions of viruses, or the inability of HIV to interact with CD8+. For determining, predicting the progress of the disease, the immunoregulatory indicator (CD4+/CD8+) has a high position. In our studies, these values highly decline in relation to the data of the control group ($P < 0.01$).

There is a concept that a progressive decrease in the immunoregulatory index CD 4/ CD 8 correlates with the progression of HIV infection.

During the study, the features of expression of markers of early lymphocyte activation - CD 25 molecules, markers of middle stages of activation - CD 71 molecules were assessed. In addition, the readiness of cells for apoptosis was assessed based on the determination of the expression level of CD 95 molecules.

Changes in T-lymphocytes in women with HIV infection are manifested by a decrease in proliferation and cloning and a violation of the differentiation of CD 4+ and CD 8+ subpopulations. All these violations are due to the loss of the ability to produce IL-2 [76; p . 56]. The results obtained indicate a decrease in the peripheral blood of women with HIV infection, both group 1 and group 2, in the content of lymphocytes expressing CD 25 molecules on their surface.

The interaction of mononuclear cells of HIV-infected patients with immune aggregates containing HIV antigens leads to a decrease in the relative number of double-positive CD71+ cells, activation markers of the middle stage. In our study, the

level of CD 71+ cells in patients of the 1st group was 21.07 ± 0.6%, in the 2nd group - 19.2 ± 0.8% compared to the control group had an insignificant difference - 23.2 ± 1.0%. At present, the main idea explaining the causes of activation of adaptive immunity cells in HIV infection is the concept based on the entry into the blood of microbial products from the genitourinary tract damaged by infection.

Immune mechanisms in this process implement and regulate the programmed course of cell death. Also, the process of apoptosis controls the activity of immunocompetent cells to antigen stimuli, determining the duration and prognosis of the immune response, forming immunological tolerance. Analysis of these cells indicates that the frequency of expression of C D -95 on them in women of the first group does not exceed (26.3-27.1% compared to the control group, where this indicator varies within 24.1-25.2%) and there is a tendency to increase in women of the second group (28.4-29.2%).

Based on the obtained results, we derived the lymphocyte activation index from the ratio of the number of early activation lymphocytes (CD 25+) and late activation stages (CD 95+) - the IAL in women in the control group was 0.88 conventional units, while in women in the 1st group this value was lower and was 0.7 conventional units, and in women in the 2nd group - 0.5 conventional units.

Therefore, IAL can be used as a prognostic criterion for immunosuppression in HIV-infected women with inflammatory diseases of the genitals, both receiving and not receiving ART. And among women receiving ART, this indicator can be used to judge the adequacy of the dose and the selected ART regimen.

In addition to the disorganization of cellular immunity, women with HIV infection and inflammatory diseases of the genital organs also have disorders in the humoral link. Along with dysregulation of the T-system, an increase in the total pool of B-lymphocytes (CD20+) was noted, which are key receptors for modulating the passage of a signal during antigen stimulation. Frequent exacerbation of the chronic process is accompanied by an increase in CD 20+ lymphocytes. It was found that the level of B-lymphocytes was significantly increased both in women of the 2nd group (34.5 ± 1.2% versus 25.9 ± 1.2% in the control, $p < 0.01$) and in women of the 1st

group (29.7 ± 1.1%, p < 0.05). At the same time, 95% of immunoglobulins are nonspecific despite the presence of the virus. In women of the 1st group, the IgG concentration was significantly increased (13.8 ± 1.6 g/l) (P < 0.005), and in patients of the 2nd group it was 1.7 times higher than in the control group - 16.2 ± 1.9 g/l with fluctuations from 12.8 to 18.5 g/l (p < 0.01). In our studies, in women of the control group, the IgA level in the blood serum ranged from 1.0 to 1.8 g/l, which averaged 1.6 ± 0.1 g/l. In the peripheral blood serum of women in group 1, the concentration of IgA was significantly increased - 1.97 ± 0.2 g / l (p < 0.05), and in patients of group 2, a more pronounced increase was observed, by 1.6 times, which on average amounted to 2.51 ± 0.3 g / l (p < 0.01). The study of the IgM level showed that in the group of women in group 1, its concentration was significantly increased, on average amounting to 1.6 ± 0.17 g / l (p < 0.05). And in women of group 2, a reliable increase in IgM by 1.4 times was observed (p < 0.05).

According to a number of authors, the main role in the development of the inflammatory process in women with HIV infection is played by the inability of the woman's immune system to localize the source of possible infectious aggression and eliminate the pathogen. Consequently, the body's resistance to infections will be largely determined by the functional state of B-lymphocytes. Pronounced disorders of B-cell immunity are associated with the inflammatory process of the genital organs and its clinical manifestation.

In women with HIV infection, a reliable increase in the CIC titer was revealed in VZG. The CIC level in women in the control group averaged 34.8 ± 1.5 conventional units. Inflammatory processes contribute to the accumulation of circulating immune complexes, which in turn aggravates this process. It was confirmed that inhibition of the phagocytic system component and imbalance of the amount of immunoglobulins in the blood serum affect the imbalance of the complement system, but the main factors are the expression of antibody synthesis, especially IgG . The property of -lymphocytes to change the formation of a group of antibodies is based on intercellular connections with the calculation of various

cytokines. The negative effect of pathogens on lymphocytes, leading to a decrease in their number, indicates the suppression of the properties of cellular immunity.

CD 4+ lymphocytes, performing their helper function, help, firstly, B cells to transform into antibody-producing plasma cells; secondly, CD 8+ lymphocytes to transform into mature cytotoxic T cells; thirdly, macrophages to carry out the effects of hypersensitivity.

In our study, we observed a significant decrease in IL -4 activity in the observation groups - 34.18±1.0 in the 2nd group and 37.5±0.9 pg/ml in the 1st group compared to the control values - 79.48±49.71 pg/ml, $p < 0.05$.

In the processes of regulation of innate and adaptive immunity, one of the main types of cytokine is IL 8, the main function of which is to regulate the antigen-dependent immune response based on its participation in stimulating the proliferation and differentiation of immune cells, including T-lymphocytes. We can assume that an increase in the content of IL8 in the blood also affects the disruption of the proliferation and differentiation of immunocompetent cells in patients with HIV infection. This condition affects the development of drug resistance in the virus under conditions of constant replication of the virus and the presence of concomitant pathologies of lower genital tract infections. Thus, in women under our observation and receiving ART, the IL -8 level was 33.3±2.1 pg/ml, and in patients who refused pathogenetic therapy - 35.45±1.78 pg/ml, compared with control values - 23.02±0.82 pg/ml, ($p \leq 0.0\ 0\ 1$).

Research into the functions of Th17 has shown that they produce IL 17, which has the functions of a strong proinflammatory cytokine, which performs an important task in protecting the body from microorganisms, fungi and autoimmune processes .

When assessing the average values of serum interleukin-17 in the groups studied (Table 4, 5), a significant increase was noted, compared with the control group, in the amount of serum interleukin-17 in individuals with human immunodeficiency virus with severe immunodepression due to a decrease in CD4+ lymphocytes below 200 μl-1, who refused to undergo ART, and this indicator was equal to 111.3 ± 11.5. pg / ml. This proves an increase in the concentration of

interleukin-17 in patients with severe immunosuppression who did not undergo ART. ART significantly inhibits viral division, which is proven by the presence of a decrease in viral load and confirmed by us - the level of IL -17 in the 1st group of patients was higher than the control values, but significantly lower in comparison with the 2nd group - 89.4±9.8 pg/ml ($p \leq 0.0\ 0\ 1$) .

During HIV, a significant decrease in Th17 is recorded, as well as in lymphoid tissues that have mucous membranes (gastrointestinal tract, respiratory tract, excretory tract). It is in this localization that Th 17 performs a significant function of regulating local microflora and limits its movement through the bloodstream. In this mechanism, the ability of interleukin 17 to stimulate the formation of enterocytes is important, which is a deterrent to migration. It follows that during HIV infection, which suppresses the formation of Th -17, leads to the destruction of mucous membranes and leads to the migration of microflora through the bloodstream. High levels of interleukin-17 in the serum of patients with the immunodeficiency virus indicate a general activation of the defense system in patients with severely suppressed immunity. Due to the control of the production of various cytokines through ART therapy, it can cause positive results in the treatment of HIV infection at late stages and in the formation of AIDS-associated lesions.

The study showed inhibition of the natural and cellular immune response due to high levels of cytokines such as IL 8, IL 17, and suppression of IL 4 production in the blood serum. In theory, this is a normal physiological response to a pathogen, but a low phagocytic response entails a disruption in the balance of cytokines and their inactivation. This pattern is observed in chronic inflammatory diseases of the genitals. High levels of IL 8 and IL 17 A in the blood serum of patients with the human immunodeficiency virus are a sign of general activation of the immune system due to a strong increase in the number of CD4+ lymphocytes in the late stages of HIV infection. There is a possibility that ART therapy with control of specific cytokines in the blood can improve the results of this therapy at different stages of HIV infection, as well as in the development of AIDS-associated lesions and concomitant inflammatory diseases of the genitals.

The algorithm we propose for the management of HIV-positive women with VZG includes: mandatory counseling during registration, a complete clinical and laboratory examination to confirm or identify the cause and location of VZG. Primary counseling includes a detailed review of ART regimens, in case of an earlier refusal to conduct ART, informing on somatic risks and, when planning reproductive tasks, obstetric risks in the future with the aim of immediately starting ART. The next stage is an immunological examination, including the determination of CD 25+, CD 95+, IL 17 A. It is necessary to calculate the lymphocyte activation index - CD 25+ / CD 95+, if this ratio is less than 0.7 conventional units and the IL 17 A level is more than 3 times higher than the standard indicators in women receiving ART, then they need to undergo preventive therapy even in the absence of signs of VZG activity. For women who have not received ART, it is necessary to immediately start ART. If this indicator is less than 0.5 conventional units, for women who have received ART, the regimens and/or doses of ART should be reviewed and treatment should be carried out by a gynecologist, and for women who have not received ART, ART should be immediately and forcibly started and treatment for VZG should be carried out with monitoring after 1 and 3 months.

Based on this, using these clinical and laboratory indicators for diagnosing immunosuppressive processes in HIV-infected women with VZG, an individual treatment strategy was determined for each patient. When considering anamnestic risk factors and the results of clinical and laboratory indicators and symptoms, it is possible to carry out timely diagnostics and, if necessary, carry out therapy for this pathology. This makes it possible to establish the degree of risk and progression of immunosuppressive processes in HIV-infected women who have consulted a gynecologist about VZG.

CONCLUSIONS

1. In the structure of gynecological diseases, condylomas were detected in 19.3% of HIV-infected women, while 23.1% of them sought help due to recurrence. High-risk human papillomavirus type 16 was detected in 22%, type 18 in 14% of patients with CIN. Colpitis was diagnosed in more than 60% of both groups, bacterial vaginosis in 23% of cases. The percentage of nonspecific colpitis prevailed - 21.5%, cervicitis and endocervicitis in 55% of cases in the comparison group, in the main group - cervicitis in 47%, chronic endometritis in 3.5% of cases, candidal colpitis in 13% of cases.

2. In HIV-infected women, when studying the innate (CD 16+ , FAN) and humoral immunity (IgA , IgM , IgG), the level of natural killer cells is accompanied by reduced activity, which corresponds to the chronicity of the process. For most of the women studied, especially group 2, it was characterized by insufficient phagocytosis activity as a result of a decrease in the activity of killer cells by 1.5 times. Humoral factors of innate immunity, an increase in the C3 component of complement, as well as the level of IFNγ, showed their inconsistency in the long-term course of the disease. The level of CRP did not depend on the duration of the disease and was significantly increased, both in women of group 1 and in group 2 by more than 2 times.

3. The study of adaptive immunity showed a decrease in the CD4+ level by 1.6 times in the 1st group and by 2.3 times in the 2nd group, as well as a decrease in the immunoregulatory index by 1.16/1.07 times. Also, suppression of early activation markers CD25+ was revealed in the 1st group - 18.5%, in the 2nd group - 14.9% and the lymphocyte activation index was derived, which in women of the control group was 0.88 conventional units, and in women of the 1st group this indicator was reduced to 0.7 conventional units, in the 2nd group - 0.5 conventional units, which indicates a decrease in adaptive immunity in women with chronic inflammatory diseases in HIV infection.

4. When studying pro- and anti-inflammatory cytokines, an increase in cytokines was revealed - IL8 almost 1.4 times exceeding the values of the control group, IL17A 3 times in group 1 and 3.8 times in group 2, respectively, inhibition of IL 4 secretion in the blood serum - 34.18 ± 1.0 in group 2 and 37.5 ± 0.9 pg / ml in group 1, which is almost 2 times lower than the control values, indicating the chronicity of the inflammatory process in women with HIV infection.

5. A program developed for the prediction and management of inflammatory diseases of the genitals in HIV - infected women in outpatient settings made it possible to determine the degree of immunodeficiency and prevent complications of inflammatory diseases of the genitals in HIV - infected women.

PRACTICAL RECOMMENDATIONS

1. In HIV-infected women with signs of inflammatory diseases of the genitals, it is necessary to determine the level of early activation lymphocytes (CD 25+) and late activation stages (CD 95+) in the peripheral blood serum to calculate the lymphocyte activation index (LAI).

2. IAL can be used as a prognostic criterion for immunosuppression in HIV-infected women with inflammatory diseases of the genitals who have or have not received ART. And among women who have received ART, this indicator can be used to judge the adequacy of the dose and the selected ART regimen.

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