

CLINICAL AND IMMUNOLOGICAL CHARACTERISTICS OF HIV-INFECTION IN DYNAMICS AGAINST THE BACKGROUND OF ANTIRETROVIRAL THERAPY AMONG PATIENTS IN POLTAVA REGION*

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ВІЛ-інфекція залишається однією з найгостріших проблем сучасної охорони здоров'я через свою соціально-медичну та демографічну значимість. Питання співставлення клініко-лабораторних характеристик з імунологічними показниками у ВІЛ-інфікованих пацієнтів, які отримують антиретровірусну терапію (АРТ) залишається актуальним, і в подальшому дасть можливість розширити уявлення про предиктори прогресування хвороби. Мета роботи – проаналізувати клініко-імунологічні характеристики ВІЛ-інфекції в динаміці на фоні АРТ з урахуванням початкового рівня CD4+ Т-лімфоцитів. Матеріали і методи. Для досягнення поставленої мети проведено когортне дослідження 181 ВІЛ-інфікованого пацієнта (чоловіків – 127, жінок – 54) віком від 21 до 55 років (середній – 34,6±0,6 роки), які спостерігались у Полтавському обласному центрі профілактики ВІЛ-інфекції та боротьби зі СНІДом від моменту постановки на облік і в динаміці на фоні АРТ. Результати та їх обговорення. У ході дослідження встановлено, що серед ВІЛ-інфікованих переважали особи молодого віку (90,0 %), чоловіки (70,2%), які залишались на момент звернення за медичною допомогою споживачами ін'єкційних наркотиків (49,2 %), із шкідливими звичками (палили – 49,2 %, зловживали алкоголем – 14,4 %) та мали досвід ув'язнення (26,5 %), в них діагностували опортуністичні інфекції, притаманні III і IV клінічним стадіям: бактеріальні (37,0 %), грибові (44,2 %), вірусні (35,4 %) та паразитарні (6,6 %), які у 31 (17,1 %) обстеженого розвинулись при рівні CD4+ Т –лімфоцитів ≥ 350 кл/мкл. Обстеження ВІЛ-інфікованих пацієнтів в динаміці показало, що на фоні АРТ у 72 (39,8 %) зі 181 хворого відмічалася клінічне прогресування ВІЛ-інфекції, з них у 21 (30 %) - при показниках CD4+ Т –лімфоцитів ≥ 350 кл/мкл.

Ключові слова: ВІЛ-інфекція, клініко-імунологічні характеристики, антиретровірусна терапія, CD4+ Т-лімфоцити.

HIV-infection is a relevant issue of the modern healthcare system due to socio-medical and demographic significance. The problem of correlation between clinico-laboratory characteristics and immunological indexes in people living with HIV-infection and obtain ART remains relevant, and the solution may help to expand the knowledge about predictors of the disease in the future. The aim of our research was to analyze the clinical and immunological characteristics of HIV-infection in dynamics against the background of ART considering the initial level of CD4+ T-lymphocytes. Patients and methods. We conducted a cohort study of 181 people living with HIV-infection – 127 male and 54 female patients, aged from 21 to 55 years (the average age 34.6±0.6 years), who underwent dispensary observation at Poltava Regional HIV/AIDS Prevention and Control Center during 2003-2017, for the purpose of evaluation of clinical and immunological characteristics of HIV-infection in dynamics against the background of ART. Results of the research and their discussion. We found that among people living with HIV, young people (90.0%) predominated; among them – males (70.2%); patients who injected drugs at the time of referral to medical care (49.2%); with bad habits (smoking – 49.2%, alcohol abuse – 14.4%) and had experience of incarceration (26.5%). They were diagnosed with opportunistic infections inherent to III and IV clinical stages of HIV-infection, including bacterial (37.0%), fungal (44.2%), viral (35.4%) and parasitic (6.6%) infections. Moreover, 24 (13.3%) patients developed the CD4+ T lymphocytes level ≥ 350 cells/ μ l. Examination of HIV-infected patients in dynamics showed that there was a clinical progression of HIV-infection against the background of ART background in 72 (39.8%) out of 181 patients, 21 of them (30%) with CD4+ T lymphocytes ≥ 350 cells/ μ l.

Keywords: HIV-infection, CD4+ T lymphocytes, antiretroviral therapy, clinic-immunological characteristics

Introduction

HIV-infection is a relevant problem of the modern healthcare system due to socio-medical and demographic significance. Thus, according to the latest data, about 37 billion people around the world live with HIV-infection [1, 2]. At the modern stage, the epidemics of HIV-infection is characterized not only by its extraordinary dynamics, but also by a high resistance to countermeasures because of late referral for medical care with the presence of serious opportunistic infections and advanced immunosuppression [3, 4]; refusal from dispensary observation; low adherence to antiretroviral therapy (ART) [5].

Efficient ART contributes to the significant reduction of morbidity and mortality of HIV-infected people. However, its prescription does not allow us to achieve the expected lifetime and quality of life of this group of patients every time [6, 7]. Although the treatment is accessible, opportunistic infections are the main cause of hospitalization and mortality among people living with HIV-infection. It has been proven that there is a direct correlation between the level of immunosuppression and the development of opportunistic infections. Thus, the universally recognized level of CD4+ T-lymphocytes, when the rapid activation of opportunistic infections occurs, is 200 cells/ μ l [8]. However, it has been found that clinical pro-

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gression of the disease occurs in some patients with a higher level of CD4+ T-lymphocytes [9]. Thus, the problem of correlation between clinic-laboratory characteristics and immunological indexes in people living with HIV-infection and receiving ART remains relevant. The problem may help to expand the knowledge about predictors of the disease in the future.

The aim of our research was to analyze the clinical and immunological characteristics of HIV-infection in dynamics against the background of ART considering the initial level of CD4+ T-lymphocytes.

Materials and methods

We conducted a cohort study of 181 people living with HIV-infection – 127 male and 54 female patients, aged from 21 to 55 years (the average age 34.6±0.6 years), who underwent dispensary observation at Poltava Regional HIV/AIDS Prevention and Control Center during 2003-2017, for the purpose of evaluation of clinical and immunological characteristics of HIV-infection in dynamics against the background of ART. The patients were observed from 2 to 14 years, with the average period of observation 4.3±0.3 years. Informed consent forms were obtained from all patients prior to any diagnostic and treatment procedure.

The diagnosis of HIV infection was made according to the International Classification of Diseases, 10th revision, and confirmed by the detection of specific serological and molecular biological markers. HIV antibodies in the blood were detected by ELISA (Labsistem test system, the Netherlands), HIV HIV-1 was detected in a polymerase chain reaction (PCR) (Real Time HIV -1 "Abbott", USA). The state of cellular immunity was assessed by the total number of leukocytes, lymphocytes and their subpopulations (absolute and relative content) by immunophenotyping with monoclonal antibodies, followed by the analysis of samples at current cytofluorimeter US FACS Conbillon (FACS Conbillon, USA).

All patients underwent a general clinical examination, and outpatient chart data were analyzed. Laboratory and follow-up studies were performed in accordance with diagnosed pathology, engaging the consultants. The analysis of the obtained clinical data and diagnosis of opportunistic infections, detection of clinical stages of HIV infection, assignment and evaluation of the effectiveness of ART were performed according to standard protocols using the classifications given in ICD-10 (WHO, 2006) [10,11].

Statistical analysis of the research results was performed using SPSS application package, version 17. The likelihood of differences in quantitative results for different groups of subjects was determined using the Student's t-test under normal distribution, and in case of distribution that differed from the normal one, – the Mann-Whitney U-test, by analyzing crosstabs using the χ² criterion. The likelihood of differences in dynamics was estimated using the McNemar criterion. Results under p = 0.05 were considered as statistically significant for all types of analysis.

Results and discussion

The research showed that people living with HIV-infection were mainly in the age groups of 20-29 and 30-39 years (140 patients (77.3%)). In general, young people form the majority of patients (163 (90.0%)). From the past medical history, it was found out that the parenteral route of HIV-infection transmission through intravenous drug injections predominated in the examined patients.

There were 121 (66.9%) patients who were infected by this route, 49 (27.1%) were infected by sexual route, and in 11 (6.0%) we could not define the possible route. In addition to injecting drug use, almost half of patients (89 (49.2%)) smoked, 26 (14.4%) regularly abused alcohol, and 48 (26.5%) had incarceration experience.

The duration of HIV-infection ranged from 1 to 20 years – 1-4 years in 64 patients (35.4%), 5-10 years in 69 patients (38.1%), and more than 10 years in 48 (26.5%). Thus, it did not exceed 10 years in the majority of cases (n=133, 73.5%).

In-depth analysis of clinical characteristics of HIV-infection demonstrated that the main reason for seeking medical care was deterioration of health. In particular, there were manifestations of asthenic-neurotic (n=99, 54.7%), feverish (n=48, 26.5%) and dyspeptic (n=32, 17.6%) syndromes, cough (n=42, 23.2%), weight loss (n=36, 19.9%), enlargement of lymph nodes (n=23, 12.7%), lesions of the skin and mucous membranes (n=21, 11.6%)

Thus, patients were seeking medical care after manifestation of the disease. This indicated late diagnostics of HIV-infection in the examined patients and was confirmed by the analysis of distribution of HIV-infection stages at the moment of dispensary enrollment at the Centre (Fig. 1).

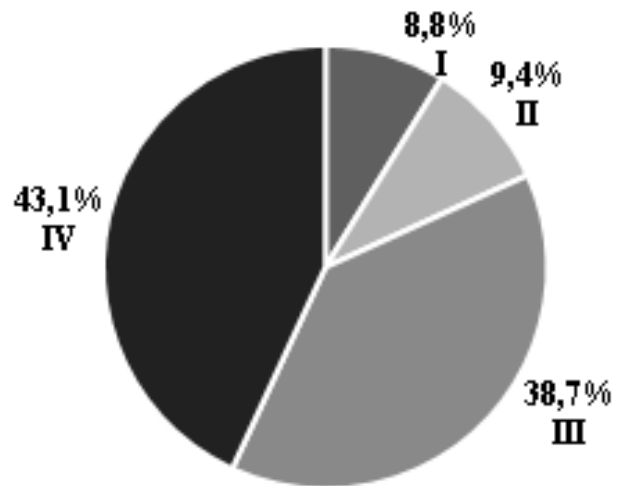


Figure. 1. Distribution of HIV-infection patients according to the stages of HIV-infection at the moment of dispensary enrollment

As can be seen from Figure 2, stages III and IV of infection were diagnosed in the vast majority of HIV-infected patients at the moment of dispensary enrollment (141 (81.8%)).

Moreover, the analysis of structure of opportunistic infections at the moment of dispensary enrollment revealed the domination of bacterial, fungal, viral and parasitic infections, which are typical of stages III and IV of HIV-infection (Table 1).

Thus, pulmonary tuberculosis was diagnosed in 31 patients (17.1%), including infiltrative, focal, and disseminated forms in 16 (8.8%), 10 (5.5%), and five (2.8%) cases respectively. Extrapulmonary tuberculosis was diagnosed in 13 (7.2%) patients, intrathoracic and peripheral lymph nodes affection – in seven observations (3.9%), including combination with pulmonary tuberculosis in 3 people (1.7%) and the combination of pleuritis with pulmonary tuberculosis in 6 patients (3.3%).

Table 1
Structure of opportunistic infections at the moment of dispensary enrollment in HIV-infected patients

Opportunistic infections	Abs. number	%
Tuberculosis	35	19.3
pulmonary	31	17.1
infiltrative	16	8.8
focal	10	5.5
disseminated	5	2.8
extrapulmonary	13	7.2
peripheral lymph nodes	2	1.1
intrathoracic lymph nodes	5	2.8
pleuritis	6	3.3
Community-acquired pneumonia	32	17.7
Pneumocystis pneumonia	3	1.7
Candidiasis	76	42.0
oropharyngeal	74	40.9
other localization (trachea, esophagus, intestines)	3	1.7
Leukoplakia of the tongue	48	26.5
Herpesvirus infections with skin and mucous membranes affection	18	9.9
shingles	9	5.0
herpes simplex	13	7.2
Cytomegalovirus infection	2	1.1
Seborrheic dermatitis	4	2.2
Cerebral toxoplasmosis	12	6.6
HIV-associated encephalopathy	5	2.8

Community-acquired pneumonia was diagnosed in 32 people (17.7%) and pneumocystis pneumonia in three (1.7%).

As can be seen from Table 1, there were 74 cases (40.9%) of oropharyngeal candidiasis that made almost half of the patients. Esophageal, intestinal and tracheal candidiasis were recorded in one (0.7%) case each.

Hairy leukoplakia, as a manifestation of reactivation of Epstein-Barr viral infection, was detected in 46 (25.4%) patients. Herpesvirus infections with lesions of the skin and mucous membranes were less frequent and were diagnosed in 18 people (9.9%), including herpes simplex in 13 (7.2%), shingles in 9 (5.0%), mixed types (simple + shingles) in 4 (2.2%) patients. Cytomegalovirus infection in the form of chorioretinitis was observed in two (1.1%) patients. The diagnosis of seborrheic dermatitis was made in four (2.2%) people.

Nervous system lesions in the form of cerebral toxoplasmosis and HIV-associated encephalopathy were reported in 12 (6.6%) and five (2.8%) patients, respectively.

Viral hepatitis, as a concomitant pathology, was diagnosed in the vast majority of HIV-infected people (n=110). 92 (50.8%) of them had chronic hepatitis C, 13 patients (7.2%) had chronic hepatitis B, and five (2.8%) – mixed hepatitis (B + C).

The most frequent changes in hemogram were monocytosis, which was recorded in 118 cases (65.2%), erythropenia in 95 (52.5%), acceleration of ESR in 74 (40.9%), thrombocytopenia – in 73 (40.3%), decrease in hemoglobin level below 100 g / l in 74 (40.9%), neutropenia in 67 (37.0%), lymphocytosis in 58 (32.0%). Leukopenia (36 cases (19.9%)), lymphopenia (17 cases (9.4%)), increase in neutrophil level (11 cases (6.1%)), and leukocytosis (15 cases (8.3%)) were less common.

The distribution of patients by the initial level of viral load of HIV and CD4 + T lymphocytes are given in Table 2.

Table 2
Initial CD4 + T-lymphocyte level and HIV viral load in HIV-infected patients, abs. number (%)

Indicator	Units of measurement	HIV-infected patients
High level of HIV viral load (>1,0x10 ⁵ copies/ml)	abs. (%)	53 (29,3)
Level of CD4+ T-lymphocytes at the moment of dispensarization cells/μl (Me (IQR))	cells/μl Me, (IQR)	170,5 (66,0-345,0)
Level of CD4+ T-lymphocytes <200 cells/μl	abs. (%)	102 (56.4)
Level of CD4+ T-lymphocytes 200-349 cells/μl	abs. (%)	36 (19.9)
Level of CD4+ T-lymphocytes 350-499 cells/μl	abs. (%)	21 (11.6)
Level of CD4+ T-lymphocytes >500 cells/μl	abs. (%)	22 (12.1)

According to the data presented in Table 2, more than a third of patients (n=53, 29.3%) had a high HIV viral load (>1.0x10⁵ copies/ml) and more than a half (n=102, 56.4%) had deep immunosuppression (CD4+ T-lymphocyte level <200 cells/μl), which confirmed the late seeking medical care of the patients examined by us.

Analysis of the structure of opportunistic infections at the time of seeking medical care, depending on the level of CD4+ T lymphocytes, revealed that the frequency of registration of opportunistic infections in most patients depended on the level of CD4+ T lymphocytes, but not always the clinical manifestations coincided with the degree of immunosuppression. Thus, opportunistic infections were registered at CD4+ T lymphocyte level <200 cells/μl almost half of the patients (n=84 (46.5%)): bacterial infections in 46 (25.4%), fungal in 50 (27.6%), viral in 34 (18.8%), parasitic in 12 (6.6%) patients. At CD4+ T lymphocyte level of 200-349 cells/μl, bacterial opportunistic infections were reported in 9 (5.0%) cases, fungal and

viral in 16 (8.8%). It drew attention to the fact that in a considerable number of the examined opportunistic infections developed at high levels of CD4+ T lymphocytes. Thus, according to individual analysis, opportunistic infections at CD4+ T lymphocyte level of ≥350 cells/μl occurred in 31 (17.1%) patients, including bacterial infections in 12 (6.6%), viral and fungal in 14 (7.7%) patients.

Dynamic observations showed that during the observation period, new opportunistic infections and diseases appeared in some of HIV-infected patients, the level of immunosuppression increased and, accordingly, the clinical stages of HIV changed. The change in the clinical stages of HIV infection during the observation period is presented in Figure 2.

As can be seen from Figure 2, the proportion of patients with stage IV increased 1.7 times and composed 71.3% (p<0.001), while the proportion of patients with I, II and III, on the contrary, decreased 2.4 times (56.9% against 23.7%, p<0.001).

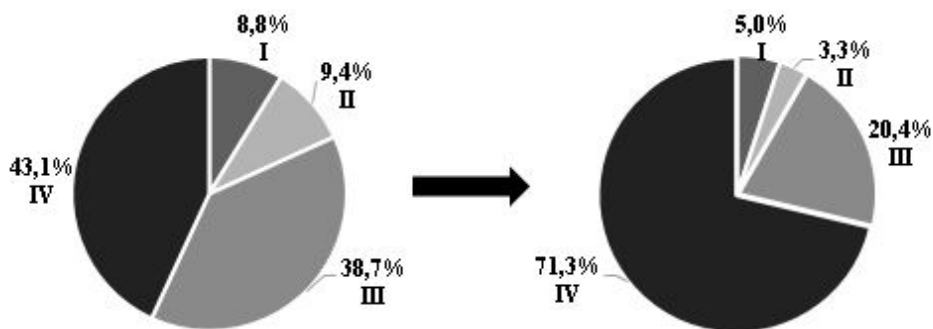


Fig. 2. Distribution of HIV-infected patients by stage of HIV infection in dynamics

The obtained data confirmed the changes in the structure of opportunistic infections. Thus, the share of all opportunistic infections was increasing in the dynamics. Pulmonary tuberculosis was registered in 66 (36.5%) patients, which is 2 times more than at the time of registration ($p < 0.001$). Extra-pulmonary tuberculosis was diagnosed in 21 (11.6%) persons, 1.6 times more than in the initial appointment ($p < 0.001$); there was also an increase in patients with lesions of mesenteric and retroperitoneal lymph nodes – 3 (1.7%) cases each, respectively, and one (0.5%) occurrence of tuberculosis meningitis.

Community-acquired pneumonia was diagnosed in 77 (42.5%) people, pneumocystis pneumonia in 6 (3.3%), which is 2.4 ($p < 0.001$) and 1.9 ($p = 0.250$) times more than at the moment of registration.

Oropharyngeal candidiasis was diagnosed in more than half of the patients (107 (59.1%)) that is 40% more than in the initial appointment ($p < 0.001$). Candidiasis of the esophagus, intestine, or trachea was recorded in eight (4.4%), two (1.1%), and one (0.6%) individuals, respectively, which is 3.5 times more than it was at the beginning of the observation ($p = 0.012$).

Hairy leukoplakia of the tongue was detected in 64 (35.4%) patients, which is 10% more than at the time of the primary treatment ($p < 0.001$). It should be noted that during the observation period the proportion of herpes virus infections with lesions of the skin and mucous membranes increased by 2.5 times and amounted to 24.3% ($p < 0.001$), among them, manifestations of herpes simplex occurred in 25 (13.8%) and shingles in 19 (10.5%) patients.

Nervous system lesions in the form of brain toxoplasmosis and HIV-associated encephalopathy were

reported in 23 (12.7%) and 13 (7.2%) patients, respectively, 1.9 and 2.8 times greater than at the time of the dispensarization ($p < 0.001$).

Analysis of the structure of opportunistic infections depending on the level of CD4+ T-lymphocytes in the dynamics showed that the proportion of people with opportunistic infections at the level of CD4+ T-lymphocytes < 200 cells/ μ l increased by 8.2% ($p < 0.001$) and was 54, 7% ($n = 99$). Bacterial infections developed in 70 (38.7%) people, 1.5 times more ($p < 0.001$) than in the beginning, viral infections in 1.4 (26.0% against 18.8%, $p < 0.001$), fungal in 1.2 (34.3% against 27.6%, $p = 0.002$), parasitic in 1.7 (11.0% against 6.6%, $p = 0.008$) times.

The number of people diagnosed with opportunistic infections at CD4+ T lymphocyte levels of 200-349 cells/ μ l also increased: bacterial in 3 (15.5% against 5.0%, $p < 0.001$), viral and fungal in 1.6 (14.4% against 8.8%, $p = 0.006$, and 13.8% against 8.8%, $p = 0.004$, respectively) times.

Also, the part of patients with opportunistic infections with CD4+ T lymphocyte rates ≥ 350 cells/ μ l increased by 1.5 times (26.0% against 17.1%, $p < 0.001$). Thus, bacterial infections were recorded in 1.9 (12.7% against 6.6%, $p = 0.004$), viral in 2.3 (17.1% against 7.7%, $p < 0.001$), fungal in 2.8 (12.7% against 7.7%, $p = 0.057$) times. It should be noted that in 24 (51.0%) patients, opportunistic infections were recorded at CD4+ T lymphocyte level ≥ 500 cells/ μ l.

Data of individual analysis of the registration of opportunistic infections depending on the level of CD4+ T-lymphocytes in patients receiving ART are presented in Figure 3.

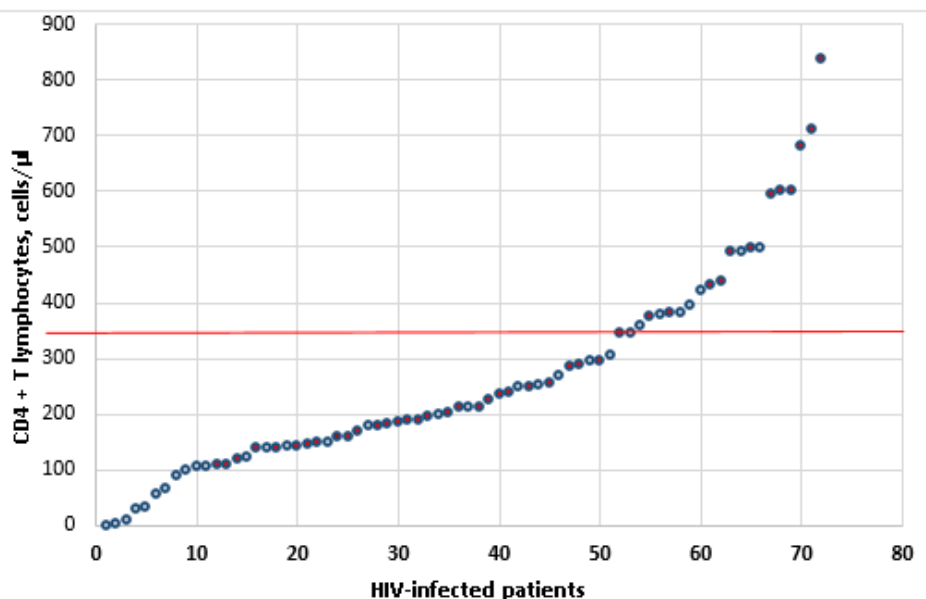


Figure 3. Analysis of the incidence of opportunistic infections depending on the level of CD4+ T-lymphocytes on ART background

According to Figure 3, disease progression with the onset of opportunistic infections on ART background was observed in 72 patients, including 21 people (30%), who had CD4+ T lymphocyte level ≥ 350 cells/ μ l.

The appearance of opportunistic infections that are typical for III-IV clinical stages of HIV infection on ART background with CD4+ T lymphocyte level ≥ 350 cells/ μ l indicates the clinical inefficiency of ART in some of our patients and confirms the need to find prognostic markers before the initiating of ART and on ART.

Conclusions

1. Among people living with HIV, young people (90.0%), males (70.2%), patients who injected drugs at the time of seeking medical care (49.2%), with bad habits (smoking - 49.2%, alcohol abuse - 14.4%) and had experience of incarceration (26.5%) were the most prevalent. They were diagnosed with opportunistic infections inherent to III and IV clinical stages of HIV-infection, including bacterial (37.0%), fungal (44.2%), viral (35.4%) and parasitic (6.6%) infections. Moreover, in 24 (13.3%) patients they developed at the CD4+ T lymphocytes level ≥ 350 cells/ μ l.

2. Examination of HIV-infected patients in dynamics showed that there was a clinical progression of HIV-infection against the background of ART in 72 (39.8%) out of 181 patients, 21 of whom (30%) with CD4+ T lymphocytes ≥ 350 cells/ μ l.

The obtained results will allow individualizing the tactics of observation of HIV-infected patients with the selection of risk group of HIV-infection progression against the background of ART with CD4+ T lymphocyte level ≥ 350 cells/ μ l.

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