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CLINICAL AND LABORATORY PREDICTORS OF ANTITOXIC IMMUNITY AGAINST DIPHTHERIA AND TETANUS IN ADULTS WITH HIV INFECTION

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Abstract. Clinical and laboratory predictors of antitoxic immunity against diphtheria and tetanus in adults with HIV infection. Revenko H.O., Mavrutenkov V.V., Chykarenko Z.O. *Antiretroviral therapy has made HIV infection a chronic controlled disease, where aspects of the immunoprophylaxis of infectious diseases have acquired important clinical significance. The goal of the study was to determine the clinical and laboratory predictors of antitoxic immunity against diphtheria and tetanus in HIV-infected adults. The study included 90 HIV-infected patients aged 22 to 60 years (main group). The control group consisted of 49 immunocompetent volunteers of the corresponding age. The levels of anti-diphtheria and anti-tetanus antibodies were determined by ELISA using the diagnostic test systems RIDASCREEN Diphtheria IgG and RIDASCREEN Tetanus IgG (R-Biopharm AG, Germany). Statistical processing was performed using the licensed software product STATISTICA v.6.1. Significant differences were found between the titers of antitoxic antibodies in HIV-infected and immunocompetent adults. According to the correlation analysis, the decrease in the titers of antidiphtheria antibodies was revealed with an increase in the age of the HIV-infected patient (rs=-0.21; p=0.05). The fact of smoking (rs=-0.31; p=0.003), lowered body weight (BMI<18.5 kg/m^2) (r_s=-0.29; p=0.006), the presence of arterial hypertension (r_s=-0.38; p<0.001), a history of bone fractures over the past 5 years (r_s=-0.38; p<0.001), anemia (r_s=-0.21; p=0.049), thrombocytopenia (r_s=-0.44; p<0.001), accelerated ESR (r_s=-0.61; p<0.001), the presence of hairy leukoplakia of the tongue (r_s=-0.23; p=0.027), frequent infections caused by herpes simplex (r_s=-0.52; p=0.003) and varicella zoster virus (r_s=-0.34; p=0.013) are associated with low levels of antidiphtheria antibodies. A direct relationship was found between the intensity of anti-diphtheria immunity and patients receiving OST (r_s=+0.54; p=0.003) and with a history of injuries with impaired skin integrity (r_s=+0.31; p=0.003). Decreased anti-tetanus immunity in HIV-infected patients was also associated with smoking (r_s=-0.48; p<0.001), decreased BMI (r_s=-0.71; p<0.001), anemia (r_s=-0.33; p=0.002), thrombocytopenia (r_s=-0.75; p<0.001), a history of bone fractures over the past 5 years (r_s=-0.67; p<0.001); the total number of HIV-associated opportunistic diseases (r_s=-0.42; p<0.001), including the presence of oropharyngeal candidiasis (r_s=-0.23; p=0.032) and hairy leukoplakia of the tongue (r_s=-0.57; p<0.001), history of Herpes Zoster in the past (r_s=-0.48; p<0.001), with frequent relapses of diseases caused by herpes simplex viruses (r_s=-0.78; p<0.001) and repeated episodes of herpes zoster (r_s=-0.74; p<0.001), as well as with pathology of the skin (r_s=-0.55; p<0.001). Protective predictors of anti-tetanus antitoxic immunity strength were established: male gender (r_s=+0.22; p=0.039), parenterally acquired HIV infection (r_s=+0.21; p=0.05), HIV-infected patients receiving OST (r_s=+0.40; p=0.041). A direct relationship was found with the decreased level of hemoglobin (r_s=+0.41; p<0.001), the increase of relative number of lymphocytes in the blood (r_s=+0.21; p=0.05), as well as with living in rural areas (r_s=+0.40; p<0.001) and the presence of injuries with impairment of skin integrity (r_s=+0.84; p<0.001). Clinical and laboratory predictors of strength of antitoxic immunity against diphtheria and tetanus in HIV-infected adults were identified, which allows us to create an individual "vaccination roadmap" for patients in this category.*

Реферат. Клініко-лабораторні предиктори напруженості антитоксичного імунітету проти дифтерії та правця в дорослих осіб з ВІЛ-інфекцією. Ревенко Г.О., Маврутенков В.В., Чикаренко З.О. *Антиретровірусна терапія привела до того, що ВІЛ-інфекція стала хронічною керованою хворобою, де аспекти імунопрофілактики інфекційних захворювань набули важливого клінічного значення. Метою дослідження було визначити клінічні та лабораторні предиктори напруженості антитоксичного імунітету проти дифтерії та правця у ВІЛ-інфікованих дорослих осіб. Обстеження проведено в 90 ВІЛ-інфікованих пацієнтів віком від 22 до 60 років (основна група). Групу контролю становили 49 імунокомпетентних добровольців відповідного віку.*

Визначення рівнів протидифтерійних і протиправцевих антитіл проводилося методом ІФА з використанням діагностичних тест-систем RIDASCREEN Diphtheria IgG і RIDASCREEN Tetanus IgG (R-Biopharm AG, Germany). Статистичну обробку проводили за допомогою ліцензійного програмного продукту STATISTICA v.6.1. Виявлені суттєві розбіжності між титрами антитоксических антитіл у ВІЛ-інфікованих й імунокомпетентних дорослих осіб. За даними кореляційного аналізу встановлено зменшення титрів антидифтерійних антитіл зі збільшенням віку ВІЛ-інфікованого пацієнта (r_s=-0,21; p=0,05). Факт тютюнопаління (r_s=-0,31; p=0,003), дефіциту маси тіла (ІМТ<18,5 кг/м^2) (r_s=-0,29; p=0,006), наявності артеріальної гіпертензії (r_s=-0,38; p<0,001), наявності в анамнезі переломів кісток за останні 5 років (r_s=-0,38; p<0,001), анемії (r_s=-0,21; p=0,049), тромбоцитопенії (r_s=-0,44; p<0,001), прискореної ШОЕ (r_s=-0,61; p<0,001), наявності волосистої лейкоплакії язика (r_s=-0,23; p=0,027), частих рецидивів інфекцій, спричинених herpes simplex (r_s=-0,52; p=0,003) та varicella zoster virus (r_s=-0,34; p=0,013) співвідносяться з низькими рівнями антидифтерійних антитіл. Установлено прямий зв'язок напруженості протидифтерійного імунітету з отриманням пацієнтами ЗПТ (r_s=+0,54; p=0,003) і з наявністю в анамнезі травм з порушенням цілісності шкіри (r_s=+0,31; p=0,003). Знижений антиправцевий імунітет у ВІЛ-інфікованих пацієнтів також ймовірно асоціюється з тютюнопалінням (r_s=-0,48; p<0,001), зниженим ІМТ (r_s=-0,71; p<0,001), анемією (r_s=-0,33; p=0,002), тромбоцитопенією (r_s=-0,75;p<0,001), наявністю в анамнезі переломів кісток за останні 5 років (r_s=-0,67; p<0,001); загальною кількістю ВІЛ-асоційованих опортуністичних захворювань (r_s=-0,42; p<0,001), в тому числі наявністю орофарингеального кандидозу (r_s=-0,23;p=0,032), волосистої лейкоплакії язика (r_s=-0,57; p<0,001), наявністю хоча б одного епізоду оперізувального герпесу в анамнезі (r_s=-0,48; p<0,001), з частими рецидивами захворювань, викликаних вірусом herpes simplex (r_s=-0,78; p<0,001), і частими рецидивами varicella zoster virus (r_s=-0,74; p<0,001), а також з патологією шкіри (r_s=-0,55; p<0,001). Позитивними предикторами напруженості антиправцевого антитоксичного імунітету встановлені: чоловіча стать (r_s=+ 0,22; p=0,039), парентеральний шлях інфікування ВІЛ (r_s=+0,21; p=0,05), отримання ВІЛ-інфікованими пацієнтами ЗПТ (r_s=+0,40; p=0,041). Виявлено прямий зв'язок з рівнем гемоглобіну (r_s=+0,41; p<0,001), відносною кількістю лімфоцитів у крові (r_s=+0,21; p=0,05), а також з проживанням у сільській місцевості (r_s=+0,40; p<0,001) і наявністю травм з порушенням цілісності шкіри (r_s=+0,84; p<0,001). Виявлені клініко-лабораторні предиктори напруженості антитоксичного імунітету проти дифтерії та правця у ВІЛ-інфікованих дорослих людей можуть створювати основу для індивідуальної «дорожної карти вакцинації» для пацієнтів цієї категорії.

Modern antiretroviral therapy (ART) has significantly increased survival rate among HIV-infected individuals, which concurrently raised the quiestion of primary care surveillance of adult HIV-infected people [1, 2, 8]. The immunosuppressed status due to HIV infection is a risk factor for morbidity and mortality caused by a number of infectious diseases, including those preventable by vaccination [3, 5]. Diphtheria and tetanus are the most striking examples of a continuing health threat worldwide. One of the contributing factors is that neither these diseases themselves nor vaccination against them leads to long-term protection [8].

HIV-infected persons are at increased risk of any infectious disease. Risk lowering strategies for the potential development of preventable infectious diseases should regard vaccine prevention as a leading component in providing support and management of all HIV-infected individuals. Reducing the incidence of infections that can be prevented by immunoprophylaxis is one of the priorities for healthcare personnel in the new era of HIV infection [1, 7, 4, 11].

Uncertainty about vaccine safety significantly impedes immunization. However, evidence suggests that inactivated vaccines, namely, diphtheria and tetanus toxoid, have a similar safety profile both among HIV-infected and HIV-uninfected persons [3, 6]. Recent studies show that the progression of HIV infection was not observed during the immunization with the above vaccines in ART recipients. Only in a cohort of HIV-infected individuals who did not receive ART, transient decreases in $CD4^+$ T lymphocyte counts and increases in HIV RNA levels can be observed, but these rates normalize within 2-4 weeks after vaccination [3, 12]. Carrying out safe, timely and effective immunizations is the most effective method of avoiding diseases that can be prevented in HIV-infected individuals [1, 9].

Studies of antitoxic immunity against diphtheria and tetanus in HIV-infected adults are very limited in the world, and have not been conducted in Ukraine, which makes the selected topic relevant.

The purpose of the study was to determine the clinical and laboratory predictors of the intensity of antitoxic immunity against diphtheria and tetanus in HIV-infected adults.

MATERIALS AND METHODS OF RESEARCH

The study involved 90 patients with HIV between the ages of 22 and 60, with an average age of 40.1±0.9 years, of which 51 (56.7%) were women, 39 were men (43.3%). Observations of HIV-infected patients were conducted on the basis of SI "Municipal Clinical Hospital No 21 named after prof. E.G. Popkova" DOR" (Dnipro), the Municipal Center of Prevention and Fight against HIV/AIDS in Dnipro.

Copying of clinical and laboratory data was carried out from medical records at the aforementioned healthcare institutions.

Laboratory study of the levels of antitoxins in the serum against diphtheria (anti-DT) and tetanus (anti-TT) toxins in the observation group was carried out at the Diagnostic Center of the Dnepropetrovsk Medical Academy of the Ministry of Health of Ukraine. Immunoassay enzyme-linked immunosorbent assay (ELISA) was used to assess RIDASCREEN Diphtheria IgG and RIDASCREEN Tetanus IgG (R-Biopharm AG, Germany) diagnostic test systems. The examination was carried out according to the manufacturer's instructions. The status of diphtheria and tetanus immunity was assessed by determining the concentration of antibodies in IU/ml. The assessment of the intensity of antitoxic immunity was carried out according to the following criteria (table 1).

Table 1

Ranging of strength of antitoxic immunity against diphtheria and tetanus (IU/ml)

Level of immunity	Anti-DT (IU/ml)	Anti-TT (MU/ml)
Protection is absent	**< 0.1**	**< 0.1**
Minimal level of protection	**0.1-0.9**	**0.1-0.5**
Median level of protection	**1.0-1.4**	**0.6-1.0**
High level of protection	**≥1.5**	**≥1.1**

The determination of HIV RNA in the blood was performed by polymerase chain reaction (PCR) with Real-time PCR detection using standardized technology with automated preparation. The quantification of lymphocyte subpopulations in peripheral blood was determined by flow cytometry using monoclonal antibodies.

The control group included 49 healthy immunocompetent volunteers of the relevant age group – mean age – 39.0±1.2 years (p=0.44 by t-test). The results of serological monitoring were copied from the materials of the State Institution "Dnipropetrovsk Regional Laboratory Center of the Ministry of Health of Ukraine", conducted on the basis of the Ministry of Health Order No 545 of 24.11.2003 "On the state of immunity of the population of Ukraine to diphtheria and tetanus".

Ethical aspects of the work were approved at the meeting of the Committee on Biomedical Ethics of the SE "Dnipropetrovsk medical academy of Health Ministry of Ukraine" (Protocol No 1 of 20.01.2016).

Statistical processing of the results was performed using the licensed computer program STATISTICA v.6.1 (Statsoft Inc., USA, Serial No. AGAR909E415822FA). Taking into account the law of distribution of quantitative data estimated by the Shapiro-Wilk criterion, parametric and non-parametric characteristics and methods of analysis were used: for the normal law - arithmetic mean (M), standard error (m), Student's t-test (t), Fisher (F); in other cases, the median (Me), the interquartile range (25%-75%), the Mann-Whitney test (U). The relationship between traits was estimated by the Spearman rank correlation coefficient (r_s) using the following criteria to evaluate the link strength: $|r_s|$ 0.1 to 0.29 is weak, 0.3 to 0.7 is moderate, and more than 0.7 is strong. The critical level of statistical significance (p) was assumed to be ≤0.05 [10].

RESULTS AND DISCUSSION

The main route of infection in 70.0% of cases (n=63) was sexual, which is generally in concurrence with the current trend, in 30.0% (n=27) the infection occurred parenterally among injecting drug users (IDUs). Among IDUs, methadone or buprenorphine 51.9% (n=14) people were receiving opioid substitution therapy (OST) with methadone or buprenorphine. By clinical stages patients with stage III-IV (according to WHO clinical classification, 2006) – 72.2% (n=65) dominated, clinical stages I-II were diagnosed in 27.8% (n=25) of HIV-infected persons. 76.7% (n=69) of those surveyed received ART and 23.3% (n=21) did not receive therapy. ART experience ranged from 1 to 11 years and averaged 2.97±0.24 years. Immediately after the diagnosis of HIV infection, ART was administered to 42.0% (n=29) of patients, 27.6% (n=19) after 1-3 years and 30.4% after 4 years or more (n=21). A high adherence to ART was observed in 69.6% (n=48) of subjects versus 30.4% (n=21) with low adherence.

Opportunistic infectious diseases were reported in all patients, with predominance of herpes zoster (n=49; 54.4%), oropharyngeal candidiasis (n=33; 36.7%), pulmonary tuberculosis (n=31; 34.4%), and herpes labialis (n=30; 33.3%). Moreover, in 44 (48.9%) people there was one disease, in 46 (51.1%) there were two or more.

More than half of the patients smoked (n=54; 60.0%), had a body weight deficit (n=58; 64.4%) and anemia (n=56; 62.2%).

Analysis of antitoxic immunity indicators revealed that HIV-infected adults did not have sufficient levels of both anti-DT and anti-TT. It was found that the median of anti-DT titers in the main group was 0.17 (0.09-0.38) IU/ml, compared to the corresponding indicator in the control group – 1.03 (0.56-1.27) IU/ml ($p<0.001$ by U-criterion). A similar situation was found with anti-TT titers, namely: the median was 0.59 (0.28–1.09) IU/ml in HIV-infected individuals, in the control group – 1.33 (1.13-1.45) IU/ml ($p<0.001$ by U-criterion), which reflects the low level of seroprevalence to diphtheria and tetanus toxin. Overall, the unprotected layer against diphtheria among the main group was 93.3% (n=84), and against the tetanus – 52.2% (n=47).

In more in-depth analysis of immunological and clinical and laboratory parameters that can affect the intensity of antitoxic immunity, the following data were obtained. Thus, according to the correlation analysis, there was established a decrease in the titers of anti-DT with increasing age of the HIV-infected person ($r_s= -0.21$; $p=0.05$), which is a consequence of immunoscence, ie "depletion" of the immune system caused by age itself and the inability to develop long-term immune memory, especially during vaccination [8]. Similarly, the fact of smoking ($r_s= -0.31$; $p=0.003$), body weight deficit (BMI<18.5 kg/m^2) ($r_s= -0.29$; $p=0.006$); as well as the presence of such serious somatic pathology as arterial hypertension ($r_s= -0.38$; $p<0.001$) and the presence of a history of bone fracture over the past 5 years ($r_s= -0,38$; $p<0.001$) are associated with low titers of antitoxic anti-diphtheria antibodies (Fig. 1).

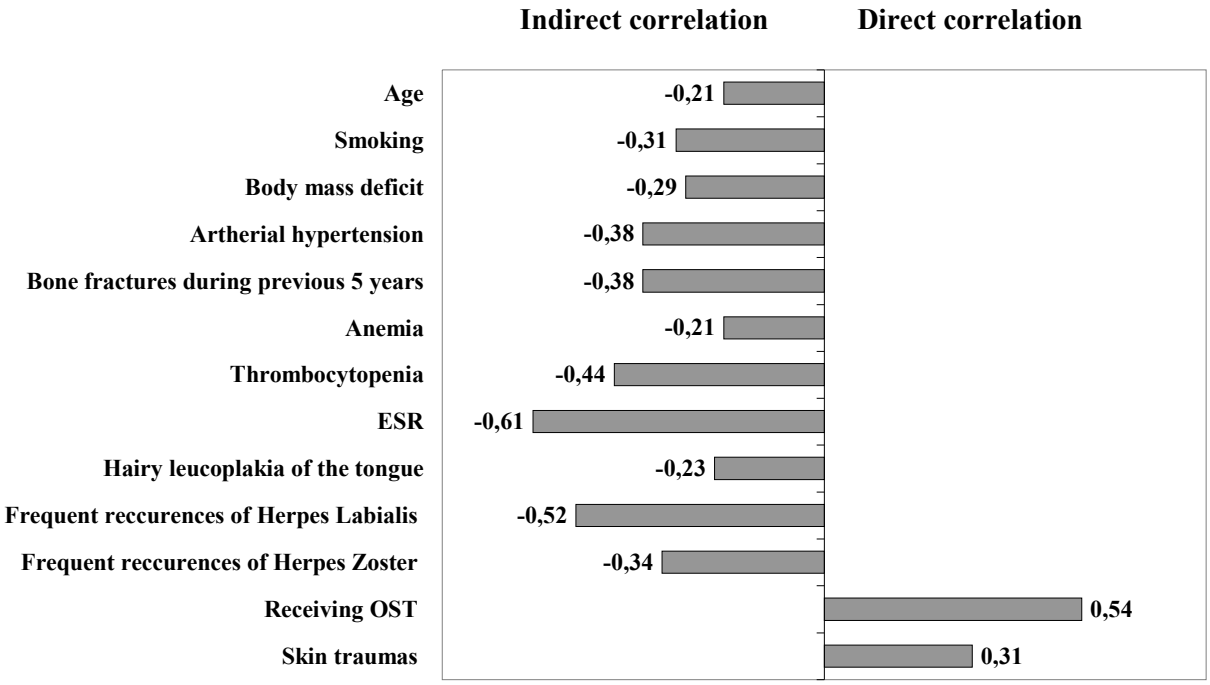

Fig. 1. Significance of correlation coefficient (rs; $p<0.05$) between clinical-laboratory parameters and the intensity of antitoxic anti-diphtheria immunity in HIV-infected adults

Laboratory indicators with low levels of protection against diphtheria include the presence of anemia in patients ($r_s= -0.21$; $p=0.049$), thrombocytopenia ($r_s= -0.44$; $p<0.001$), increased ESR ($r_s= -0.61$; $p<0.001$). Among HIV-related diseases, it should be noted that hairy leukoplakia of the tongue ($r_s= -0.23$; $p=0.027$), frequent recurrences (2 times a year and more) of infections caused by herpes simplex viruses ($r_s= -0.52$; $p=0.003$) and varicella zoster virus ($r_s= -0.34$; $p=0.013$) correlate with low levels of anti-diphtheria antibodies. Conversely, a moderate correlation was obtained between the intensity

of antidiphtheric immunity with taking of OST by the patients (r_s= +0.54; p=0.003) and with a history of injuries with impaired skin integrity (r_s= +0.31; p=0.003).

However, our study showed that the clinical stage of HIV infection (r_s=0.04; p=0.697), the level of $CD4^+$ T-lymphocytes (r_s= -0.12; p=0.279), B-lymphocytes (r_s= -0.12; p=0.280) viral load (r_s= +0.08; p=0.474), ART intake (r_s= +0.07; p=0.510) and adherence to ART (r_s= +0.04; p=0.677) had no significant relationship with the intensity of anti-diphtheria immunity.

Analyzing the strength of antitetanus immunity, it can be said that the reduced antitetanus immunity in HIV-positive individuals is also likely to be associated with smoking (r_s= -0.48; p<0.001), with reduced BMI (r_s= -0.71; p<0.001), anemia (r_s= -0.33; p=0.002), thrombocytopenia (r_s= -0.75; p<0.001), history of bone fractures over the past 5 years (r_s= -0.67; p<0.001); total number of HIV-associated infectious diseases (r_s= -0.42; p<0.001), including the presence of oropharyngeal candidiasis (r_s= -0.23; p=0.032), hairy leukoplakia of the tongue (r_s= -0.57; p<0.001) and herpes zoster (r_s= -0.48; p<0.001), with frequent relapses caused by herpes simplex viruses (r_s= -0.78; p<0.001) and varicella zoster virus (r_s= -0.74; p<0.001), as well as with various skin pathologies (pyoderma, seborrheic dermatitis, etc.) – r_s= -0.55; p<0.001 (Fig. 2).

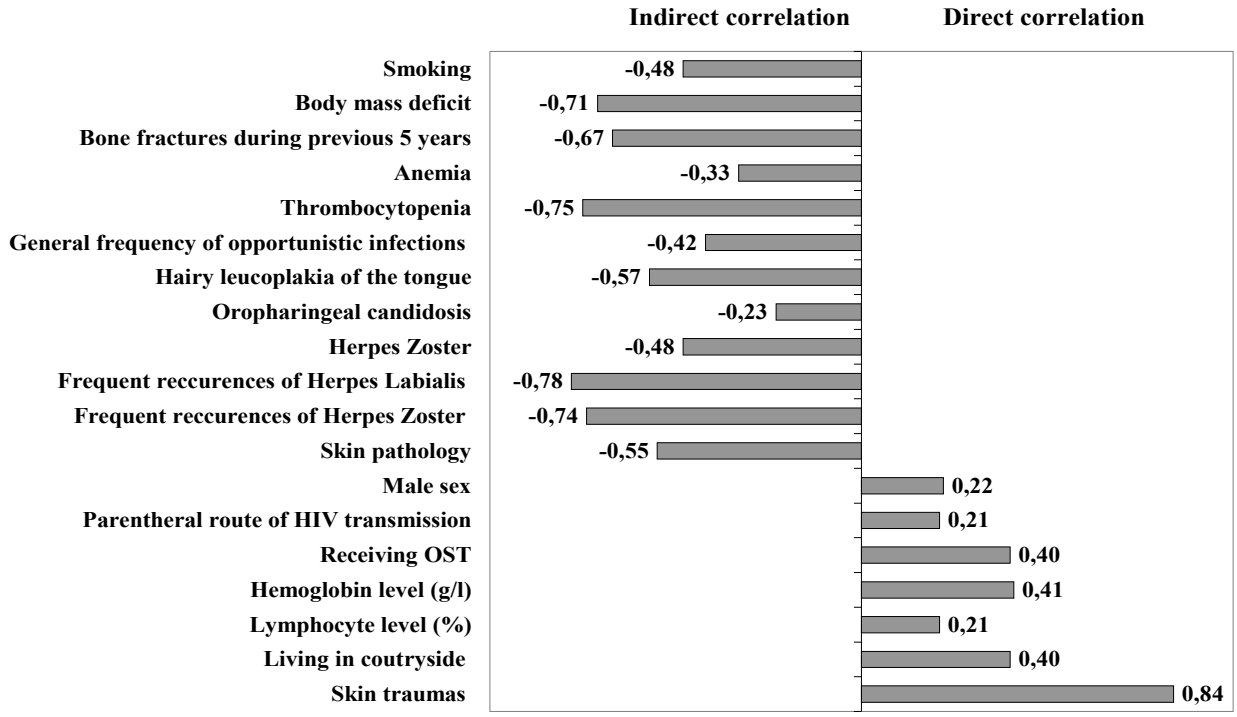

Fig. 2. Significance of correlation coefficient (r_s, p<0.05) between clinical laboratory parameters and the intensity of antitoxic immunity in HIV-infected adults

Moreover, in contrast to the correlations of the above indicators that reduce anti-diphtheria immunity (body weight deficiency, thrombocytopenia, frequent relapses of herpetic infection), the tightness of correlation with seroprevalence to tetanus was stronger ($|r_s|$>0.7).

Protective predictors of strength of anti-toxic antitetanus immunity have been established – male (r_s= +0.22; p=0.039), parenteral route of HIV infection (r_s= +0.21; p=0.05), taking of OST by HIV-positive persons (r_s= +0.40; p=0.041). There was a direct relationship with hemoglobin level (r_s= +0.41; p<0.001) and relative lymphocyte count in the blood (r_s= +0.21; p=0.05). It is also worth pointing out the interesting fact obtained regarding the direct correlation between the intensity of anti-toxic anti-tetanus immunity and living in the countryside (r_s= +0.40; p<0.001), various injuries with impaired skin integrity (r_s= +0.84; p<0.001). One of the possible assumptions that explains this immunological paradox is episodes of unintentional infection with minor (booster) doses of tetanus toxin at home,

which, in the end, helps maintain the intensity of specific immunity. But in our opinion, such "wild" immunization is unacceptable, because sooner or later it can provoke disease. That is, an immunocompromised macroorganism is able to synthesize humoral antibodies. Also in favor of this is the fact that individuals who received antitetanus toxoid (n=25; 27.8%) in the last five years, due to trauma, have higher antitetanus immunity (r_s= +0.52; p<0.001).

As in the study of anti-diphtheria immunity, it was found that the clinical stage of HIV infection (r_s= -0.03; p=0.805), the level of $CD4^+$ T-lymphocytes (r_s= -0.08; p=0.458), B-lymphocytes (r_s= -0.09; p=0.392), viral load (r_s= -0.07; p=0.489), receiving ART (r_s= +0.10; p=0.336) and adherence to ART (r_s= +0.03; p=0.779) had no significant relationship with the intensity of antitetanus immunity.

The similarity of trends in the rates of anti-diphtheria and anti-tetanus immunity in HIV-positive individuals is due to the direct moderate relationship between them – r_s= +0.392; p=0.0002, which is explained by the combined content of toxoids in the composition of the vaccine, since, as a rule, the prevention of these diseases is carried out at the same time (Fig. 3).

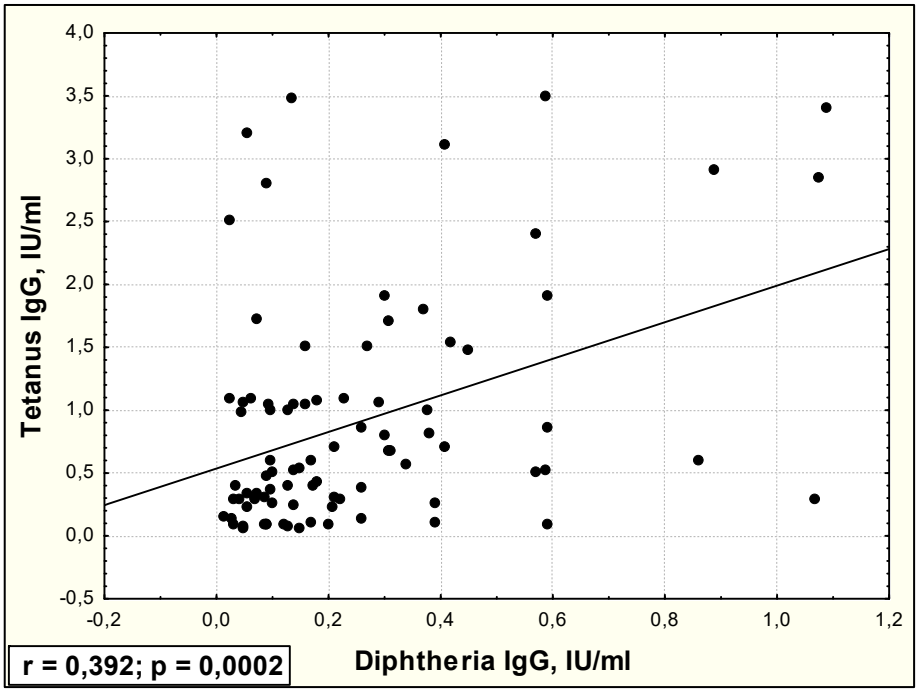

Fig. 3. Correlation between the indicators of antitoxic immunity against diphtheria and tetanus

It is significant that some discoordination has been established between the main indicative laboratory parameters for HIV infection and the intensity of anti-diphtheria and antitetanus immunity.

CONCLUSIONS

Observation results showed that:

1. Strength of antitoxic immunity against investigated infectious diseases in HIV-infected adults, namely: median anti-diphtheria antibodies – 0.17 (0.09–0.38) IU/ml and against tetanus – 0.59 (0.28–1.09) IU/ml was significantly lower than in immunocompetent subjects (p<0.001 by U-criterion).
2. The consistency of predictors and indicators of antitoxic immunity against diphtheria and tetanus (rs=+0.392; p=0.0002) allows us to extrapolate the results of the studies to each other.
3. It is possible to predict the intensity of antitoxic immunity against diphtheria and tetanus without additional specific studies, which is of economic and practical importance.
4. The identified clinical and laboratory predictors of antitoxic immunity may serve as important indicators for further development of a "roadmap for vaccination" of HIV-infected patients.

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