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PREDICTORS OF STRENGTH OF ANTITOXIC ANTI-TETANUS IMMUNITY IN HIV-INFECTED ADULTS

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Annotation. *The aim of the study was to assess the intensity of immunity against tetanus in HIV-infected adults and to investigate its relationship with key clinical and laboratory indicators to determine the predictors of the integrated use of these factors. Significant differences were found between the titers of antitoxic antibodies in HIV-infected and immunocompetent adults. Clinical and laboratory predictors of strength of antitoxic immunity against tetanus in HIV-infected adults have been identified, which allows us to create an individual "vaccination roadmap" for patients in this category.*

Keywords: *HIV-infection, tetanus, immunity, adults.*

The work is a fragment of the research of the Department of Infectious Diseases of the State Institution "Dnipropetrovsk medical academy of Health Ministry of Ukraine": "Epigenetic factors of development of the diseases associated with persistent infections in children and adults", state registration number 0117U004785.

Introduction. Immunization of adults in developed countries is a priority in health policy. Age and concomitant pathology increase the risk of susceptibility to infectious diseases [1, 2, 3, 4]. Advances in antiretroviral therapy (ART) have led to HIV becoming a latent infection and the life expectancy of immunocompromised individuals is not different from that of immunocompetent individuals, so priority should be given to primary care for HIV-infected adults. Namely vaccination should be a critical important component for ensuring the health of people living with HIV [5, 6, 7, 8, 9]. Tetanus is the clearest example of the constant threat to health around the world. In this disease there is no long-term protection. In the adult population, the risk of contracting tetanus is strongly associated with drug use [10]. Currently, the incidence of tetanus in Ukraine is 0.01-0.02 per 100 thousand population [11]. Thus, tetanus is a disease that is effectively controlled by immunoprophylaxis [5, 6, 12, 13].

Studies of antitoxic immunity against tetanus in HIV-infected adults in the world are very limited, and in Ukraine are conducted for the first time, which determines the relevance of the chosen topic.

The aim is to assess the strength of immunity against tetanus in HIV-infected adults

and to investigate its relationship with the main clinical and laboratory indicators to determine the predicting possibilities of the integrated usage of these factors.

Materials and methods. The study included 90 patients with HIV aged 22 to 60 years, the average age was 40.1±0.9 years, of which women were 51 (56.7%), men - 39 (43.3%) persons. Surveillance of HIV-infected patients was conducted on the basis of SE «Municipal Clinical Hospital # 21 named after prof. E.G.Popkova» SRC" (Dnipro), "Municipal Center for HIV/AIDS Fight and Prophylaxis", Dnipro.

Clinical and laboratory data were copied from medical records in the above-mentioned health care facilities.

Laboratory study of serum antitoxin levels against tetanus toxin in the observation group was conducted at the Diagnostic Center of the SI «Dnipropetrovsk medical academy of the Ministry of Health of Ukraine».

Methods for determining specific antibodies. RIDASCREEN Tetanus IgG diagnostic test systems (R-Biopharm AG, Germany) were used to assess the intensity of immunity against tetanus by enzyme-linked immunosorbent assay (ELISA). The test was performed according to the manufacturer's instructions. The appropriate antigen (tetanus toxin) is applied to the surface of the strips of the microplate. Antibodies contained in a patient's blood samples bind to antigens and are detected during incubation with enzyme-labeled antibodies (conjugates). The enzyme converts the colorless substrate (H2O2/ TMB) to the final blue product. The enzymatic reaction was stopped by the addition of sulfuric acid, after which the blue color changed to yellow. The final measurement was performed on an enzyme-linked immunosorbent photometer at a wavelength of 450 nm using a reference wave length ≥620 nm. The state of immunity against tetanus was assessed by determining the concentration of antibodies in IU/ml. Table 1 provides recommendations for vaccination against tetanus depending on the levels of antitoxic antibodies (according to the manufacturer's instructions).

All the patients were divided into 2 groups, depending on the intensity of antitoxic anti-tetanus immunity. Group I included 47 (52.2%) patients with no and minimum level of protection, group II included 43 (47.8%) persons with medium and high level of protection.

Table 1

Ranking of the intensity of antitoxic immunity against tetanus (IU/ml)

Level of anti-tetanus antibodies IgG (IU/ml)	Level of protection	Recommendations for vaccination
< 0.1	No protection	Basic immunization
0.1-0.5	Minimum level of protection	Booster immunization
0.6-1.0	Average level of protection	Control after 2 years
≥1.1	High level of protection	Control after 5-10 years

Determination of HIV RNA in the blood was carried out by the method of polymerase chain reaction (PCR) with detection in real time (Real-time PCR) by standardized technology with automated preparation. Determination of quantitative indicators of

subpopulations of lymphocytes in peripheral blood was determined by flow cytometry using monoclonal antibodies.

The control group included 49 healthy immunocompetent volunteers of the appropriate age group, mean age was 39.0±1.2 years (p=0.44 by t-test) and gender composition was 26 (53.1%) women and 23 (46.9%) men (p=0.68 by criterion $\chi 2$). Copying of serological monitoring results was carried out from the materials of the Dnipropetrovsk Regional Laboratory Center of the Ministry of Health of Ukraine, carried out on the basis of the order of the Ministry of Health № 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 commission on biomedical ethics of the SI «Dnipropetrovsk medical academy of the Ministry of Health of Ukraine» (Protocol № 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 № AGAR909E415822FA). Taking into account the law of distribution of quantitative data, estimated by the Shapiro-Wilk criterion, parametric and nonparametric characteristics and methods of analysis were used: for normal law – arithmetic mean (M), standard error (m), Student's criteria (t) and Fisher (F); in other cases - median (Me), interquartile range (LQ-HQ), Mann-Whitney test (U). The comparison of relative values was performed according to Pearson's test Chi-square ($\chi 2$) and two-sided Fisher's exact test (FET). To compare values in groups of patients with different levels of antibody titers, the odds ratio (OR) was determined with a 95% confidence interval (95% CI). The rate was calculated as the ratio of the chances of having low/no anti-tetanus immunity to the chances of having a medium/high level of protection. If the value of OR is from 0 to 1, it corresponds to a decrease in chances (risk); at indicators OR = 1 - lack of effect; with OR higher than 1 - increased risk.

The relationship between traits was assessed by Spearman's rank correlation coefficient (rs) using the following criteria to assess the strength of the correlation: |rs| from 0.1 to 0.29 - weak correlation, from 0.3 to 0.7 - moderate, more than 0.7 - strong. The critical level of statistical significance (p) was taken as ≤ 0.05 [14].

Results. Among the cohort of observation in the anamnesis, no one had tetanus. According to the vaccination history, all subjects received a course of vaccination against diphtheria and tetanus in childhood, namely: 3 doses of vaccination and 3 doses of revaccination (the last at 14 years - according to previous national vaccination schedules). It should be noted that 25 people (27.8%) underwent post-exposure prophylaxis for tetanus due to injuries during the last 5 years. We found that the median anti-tetanus antibody was 0.59 (0.28-1.09) IU/ml in HIV-positive individuals, which is 2.3 times lower than in the control group - 1.33 (1.13-1.45) IU/ml ($p<0.001$ by U-test).

For in-depth analysis, all patients with HIV infection were divided into 2 groups taking into account the intensity of antitoxic anti-tetanus immunity (Table 2). Thus, the median of tetanus IgG in the group with no and minimal levels of protection (group I) was 0.28 (0.10-0.39) IU/ml, which is 5.3 times less than in the group with medium and high levels of tetanus IgG (group II) - 1.48 (1.00-2.50) IU/ml ($p<0.001$ by U-test).

Table 2

Mean levels of antibodies against tetanus in groups of HIV-infected adults with varying degrees of antitoxic immunity to tetanus immunity (Me (LQ-HQ))

Indicator	Group I (n=47)	Group II (n=43)	The difference between the groups (U-test)
The level of anti-tetanus antibodies IgG (IU/ml)	0.28 (0.10-0.39)	1.48 (1.00-2.50)	p<0.001

Comparative characteristics of patients of the I and II groups are given in table 3.

Table 3

Leading phenotypic and clinical characteristics of HIV-infected patients in the study groups (abs.% or M±m)

Indicator		Group I (n=47)	Group II (n=43)	Difference between groups (p)	OR (95% CI)
Average age, years		39.9±1.4	40.5±1.2	*0.742	0.99 (0.95-1.04)
Sex:	male female	15/31.9 32/68.1	24/55.8 19/44.2	0.022	0.37 (0.16-0.88) 2.69 (1.14-6.36)
Path of infection:	parenteral sexual	10/21.3 37/78.7	17/39.5 26/60.5	0.059	0.41 (0.16-1.05) 2.42 (0.96-6.12)
Obtaining SMT:	yes, n=14 no, n=13	3/30.0 7/70.0	11/64.7 6/35.3	0.081	0.23 (0.04-1.25) 4.28 (0.80-22.93)
Clinical stages of HIV infection:	I-II, n=25 III-IV, n=65	15/31.9 32/68.1	10/23.3 33/76.7	0.360	1.55 (0.61-3.95) 0.65 (0.25-1.65)
Getting ART:	yes, n=69 no, n=21	35/74.5 12/25.5	34/79.1 9/20.9	0.606	0.77 (0.29-2.07) 1.3 (0.48-3.47)
Number of opportunistic diseases:	2 or more 1 disease	31/66.0 16/34.0	15/34.9 28/65.1	0.003	3.62 (1.51-8.63) 0.28 (0.12-0.66)
VZV infection:	yes, n=49 no, n=41	34/72.3 13/27.7	15/34.9 28/65.1	<0.001	4.88 (1.99-11.95) 0.20 (0.08-0.50)
Recurrences of VZV infection, n= 49:	1 time per year, n=15 2 times and>, n=34	2/5.9 32/94.1	13/86.7 2/13.3	**<0.001	0.01 (0.0-0.08) 104.0 (13.21-818.7)
Hairy leukoplakia of the tongue:	yes, n=38 no, n=52	30/63.8 17/36.2	8/18.6 35/81.4	<0.001	7.72 (2.92-20.40) 0.13 (0.05-0.34)
Oropharyngeal candidiasis:	yes, n=33 no, n=57	20/42.6 27/57.4	13/30.2 30/69.8	0.226	1.71 (0.72-4.08) 0.59 (0.24-1.40)
Tuberculosis:	yes, n=31 no, n=59	14/29.8 33/70.2	17/39.5 26/60.5	0.331	0.65 (0.27-1.56) 1.54 (0.64-3.69)
Herpes labialis:	yes, n=30 no, n=60	15/31.9 32/68.1	15/34.9 28/65.1	0.765	0.88 (0.36-2.10) 1.14 (0.48-2.75)

Recurrences of Herpes labialis, n= 30:	1 time per year, n=20 2 times and>, n=10	5/33.3 10/66.7	15/100.0 0/0.0	**<0.001	0.02 (0.0-0.34) 59.2 (2.95-1187.8)
Anemia:	yes, n=56 no, n=34	37/78.7 10/21.3	19/44.2 24/55.8	<0.001	4.67 (1.86-11.75) 0.21 (0.09-0.54)
Thrombocytopenia:	yes, n=28 no, n=62	26/55.3 21/44.7	2/4.7 41/95.3	**<0.001	25.38 (5.49-117.4) 0.04 (0.01-0.18)
Body mass index:	reduced, n=58 normal, n=32	44/93.6 3/6.4	14/32.6 29/67.4	<0.001	30.38 (8.02-115,1) 0.03 (0.01-0.12)
Skin injuries:	yes, n=44 no, n=46	3/6.4 44/93.6	41/95.3 2/4.7	**<0.001	0.003 (0.0-0.02) 300.7 (47.79-1891.5)
Vaccination of TT for the last 5 years:	yes, n=25 no, n=65	1/2.1 46/97.9	24/55.8 19/44.2	**<0.001	0.02 (0.0-0.14) 58.1 (7.33-460.7)
Accommodation:	city, n=53 village, n=37	35/74.5 12/25.5	18/41.9 25/58.1	0.002	4.05 (1.66-9.89) 0.25 (0.10-0.60)
Tobacco smoking:	yes,n=54 no, n=36	38/80.9 9/19.1	16/37.2 27/62.8	<0.001	7.13 (2.74-18.50) 0.14 (0.05-0.36)

Notes: OR - the ratio of the chances of having low/no anti-tetanus immunity to the chances of having a medium/high level of protection;
p is the level of significance of differences between groups according to Student's criteria (*), Fisher's exact criterion (**) and χ2-Pearson

As can be seen from Table 3, the study groups did not differ in the age of patients (pt=0.742). At the same time, significant differences in gender composition were found (pχ2=0.022), namely: the number of men prevailed among patients of the second group (55.8%), and in the first group their share was 31.9%. That is, the risk of having low/no anti-tetanus immunity in HIV-infected male patients is low - OR=0.37; 95% CI 0.16-0.88, which may be due to other factors. The clinical stages were dominated by patients with stage III-IV (according to the WHO clinical classification, 2006) - 65 (72.2%), and their share did not differ significantly among patients of the first (68.1%) and second (76.7%) of the group (pχ2=0.360). 69 subjects (76.7%) received ART, the other 21 (23.3%) patients did not receive therapy, without a significant difference between the study groups (pχ2=0.606). ART experience ranged from 1 to 11 years, with an average of 2.97±0.24 years, and also did not differ significantly between groups (pt=0.631).

The length of stay of patients on the follow-up register ranged from 1 to 15 years and averaged 5.22±0.40 years: patients of the first group were registered for 5.13 ± 0.55 years against 5.33 ± 0.59 years in patients of the II group (pt=0.806). By HIV transmission, patients were distributed as follows: 63 people (70.0%) were sexually infected, which is now dominant in the population of HIV-infected people, and 27 (30.0%) - parenterally among injecting drug users (IDUs). It was found that the number of IDUs among patients with high and medium titers of anti-tetanus antibodies tended to

be more common than in patients of group I - 39.5% vs. 21.3%, which is confirmed by a weak relationship rs=0.20 (p=0.06).

Among IDUs, 14 (51.9%) were on substitution maintenance therapy (SMT) using methadone or buprenorphine. It was noticed that people on SMT had higher titers of anti-tetanus antibodies - 64.7% compared to 30.0% of people in group I, which is a trend ($p\chi2=0.081$).

HIV-indicative diseases were registered in all patients, among which shingles prevailed (54.4%), hairy leukoplakia of the tongue (42.2%), oropharyngeal candidiasis (36.7%), pulmonary tuberculosis (34.4%) and herpes labialis (33.3%). Isolated cases of onychomycosis (4.4%), toxoplasmosis of the brain (3.3%) and pneumocystis pneumonia (2.2%) were recorded. Moreover, 44 (48.9%) people had one disease, 46 (51.1%) had two or more. One opportunistic disease was probably more common in patients of group II (65.1%) against group I (34.0%) ($p\chi2=0.003$). The calculation of the odds ratio showed that the risk of having low/no anti-tetanus immunity is 3.62 times (95% CI 1.51-8.63) higher if the patient has two or more opportunistic diseases, which is confirmed by the relationship of medium strength - rs=0.31 (p=0.003).

An in-depth study of HIV-indicative diseases revealed that in the first group of observation shingles (72.3%) occurred significantly more often than in the second group (34.9%) at $p\chi2<0.001$. The calculation of the odds ratio showed that the risk of having low / no anti-tetanus immunity increases 4.88 times (95% CI 1.99-11.95) in the presence of shingles, which is confirmed by the relationship of medium strength - rs=0.38 (p<0.001). Moreover, in persons with recurrent VZV infection relapse of shingles more than once a year was also observed in group I most often (94.1%) compared with patients of group II (13.3%) (OR = 95.0; 95% CI 13.21-818.7) with a significant difference between the groups (pFET<0.001), as evidenced by the strong correlation rs=0.81 (p<0.001).

Both groups probably differed in the presence of hairy leukoplakia of the tongue ($p\chi2<0.001$): the first group dominated in terms of the presence of this pathology (63.8%) over the second group (18.6%) (OR=7.72; 95% CI 2.92-20.40), which shows the relationship of medium strength - rs=0.46 (p<0.001).

Examining the contingent with manifestations of oropharyngeal candidiasis, it was found that the groups did not differ in the presence of the specified nosology ($p\chi2=0.226$). There was no significant difference between the groups of patients with regard to pulmonary tuberculosis ($p\chi2=0.331$), which was observed in one third of the subjects (n=31 - 34.4%). At the same time, focal and infiltrative forms of tuberculosis were diagnosed in 11 (35.5%) people, and disseminated - in 20 (64.5%).

Clinical manifestations of simple herpes infection were registered in one third of patients in both groups - in 31.9% and 34.9% in groups I and II, respectively ($p\chi2=0.765$). At the same time, it was found that in 66.7% of HIV-infected people with recurrent HSV-infection and low/no anti-tetanus immunity relapse of labial herpes was observed 2 or more times a year, while in group II recurrences were observed no more often 1 once a year (pFET <0.001), which is confirmed by a strong correlation rs=0.71 (p<0.001).

Anemia was probably more common in patients of group I (78.7%) compared with

group II (44.2%) at pχ2<0.001. That is, the presence of anemia increases the chances of having low/no anti-tetanus immunity 4.67 times (95% CI 1.86-11.75), which shows a relationship of medium strength - rs=0.36 (p<0.001).

Thrombocytopenia was significantly more common among the group I group (55.3%) compared with group II (4.7%) at pFET<0.001. In other words, the presence of thrombocytopenia increases the chances of having low/no immunity against tetanus by 25.38 times (95% CI 5.49-117.4).

The relationship between the average strength between the absent or minimum level of protection and BMI - rs =0.64 (p<0.001). The vast majority of patients in group I (93.6%) were underweight, while among patients in group II decreased BMI was observed in only a third (32.6%) of patients (pχ2<0.001). The mean BMI in groups I and II were 17.8±0.1 kg/m2 and 19.0±0.2 kg/m2, respectively (pt<0.001). Calculation of the odds ratio showed that the risk of having low/no tetanus immunity in the presence of body weight deficit increases 30.38 times (95% CI 8.02-115.1).

Given the possibility of various injuries with a violation of the integrity of the skin in the home and household, we have traced this relationship with the strength of antitoxic anti-tetanus immunity. It was found that HIV-infected persons who did not receive skin injuries prevailed among patients of the first group (93.6%), while in the second group their share was 4.7% (OR=300.7 95% CI 47.79-1891.5) at pFET<0.001. Due to such injuries, 44 people (women - 18, men - 26, pχ2=0.088) had to receive post-exposure prophylaxis of tetanus with tetanus toxoid (TT) and, therefore, have a medium or high level of protection, as evidenced by the strong link between these factors - rs=0.89 (p<0.001). At the same time, only 25 out of 44 patients (56.8%) received tetanus vaccination during the last 5 years, more often men (18 out of 26 people - 69.2%) than women (7 out of 18 people - 38.9%) with pχ2=0.046, as well as patients of the second group - 24 (55.8%) against 1 (2.1%) in the first group (pFET<0.001), which increased the chances of reliable tetanus protection (OR=58,1; 95% CI 7.33-460.7). In other words, HIV-infected people are able to synthesize humoral antibodies.

The correlation of average strength between the level of tetanus immunity and the place of residence – rs=0.33 (p<0.001). Persons living in the city predominated in group I (74.5%), while in group II the percentage of urban residents was 41.9% (pχ2=0.002). The calculation of the odds indicator showed that the risk of having low/no anti-tetanus immunity in people living in the city increases 4.05 times (95% CI 1.66-9.89). This statement directly or indirectly defeats the fact of skin injury in the home or household. That is, not all individuals who received injuries with impaired skin integrity received post-exposure prophylaxis against tetanus, but have protective antibody titers because they received minor doses of tetanus toxin at the time of injury.

Regarding the fact of smoking, significant differences were found in 2 groups of the study (pχ2 <0.001). Thus, smokers were probably more common in group I (80.9%) than in group II (37.2%). That is, the presence of smoking increases the risk of having low / no anti-tetanus immunity by 7.13 times (95% CI 2.74-18.5), which is confirmed by the relationship of medium strength - rs=0.44 (p<0.001).

Comparative analysis of data from HIV-infected adult patients with varying degrees of intensity of antitoxic anti-tetanus immunity showed some differences in laboratory parameters (Table 4).

Table 4

Mean levels of basic laboratory parameters in adult patients with HIV infection and varying degrees of antitoxic immunity (M±m or Me (LQ-HQ))

Index	I group (n=47)	II group (n=43)	Difference between the groups (p)
Hemoglobin (g/l)	112.4±1.4	122.0±1.7	<0.001
Leukocytes (g/l)	5.89±0.30	5.60±0.26	0.478
Lymphocytes (g/l)	2.09±0.12	2.18±0.14	0.617
Lymphocytes (%)	36.2±1.7	39.4±1.7	0.187
ESR (mm/hour)	17.7±0.6	17.1±0.7	0.562
Platelets (g/l)	149.0±4.2	194.0±4.9	<0.001
T-lymphocytes (CD3+) (cells/µl)	1370.0 (830-1731)	1148.0 (913-1548)	*0.265
T-lymphocytes (CD3+) (%)	76.0 (67-83)	75.0 (67-81)	*0.583
T-helpers (CD4 +) (cl/µl)	401.0 (211-615)	285.0 (155-438)	*0.166
T-helpers (CD4+) (%)	21.0 (14.0-29.1)	20.0 (12.0-25.8)	*0.314
B-lymphocytes (CD19+) (g/l)	0.17 (0.10-0.25)	0.14 (0.10-0.25)	*0.660
B-lymphocytes (CD19+) (%)	8.50 (5.90-10.90)	8.50 (5.10-10.20)	*0.351
HIV RNA (VL) (copies/µl)	40.0 (40.0-10405.0)	40.0 (40.0-1452.0)	*0.326
Log10 VL (copies/µl)	1.60 (1.6-4.02)	1.60 (1.6-3.16)	*0.326

Note. p - the level of significance of differences between groups according to the criteria of Student and Mann-Whitney (*)

Thus, the average hemoglobin level of 122.0±1.7 g/l was higher in individuals with high titers of anti-tetanus antibodies compared to the group of adults with minimal/ absent levels (112.4±1.4 g/l) (pt<0.001), which confirms the relationship of medium strength - rs=0.41 (p<0.001). Thrombocytopenia, namely 149.0±4.2 g/l, was more often observed among patients of group I compared with persons of group II, where a normal level of platelets (194.4±4.9 g/l) was recorded. (pt<0,001), which is confirmed by a strong correlation between these factors - rs=0.70 (p<0.001).

In order to determine the immunological features of a high level of tetanus immunity compared to the average level of protection, we divided the second group of patients in

the main group into 2 subgroups: IIa - HIV-infected individuals with average titers of tetanus antibodies (n=21) and IIb - individuals with high titers (n=22). The analysis showed that the average number of lymphocytes (G/l) in the blood was significantly higher in patients of subgroup IIb (pt=0.049), ie a high level of tetanus protection directly correlates with the production of lymphocytes - rs=0.30 (p=0.05) (Table 5).

Table 5

Mean levels of lymphocytes in the blood of people with medium and high levels of tetanus immunity (M±m or Me (LQ-HQ))

Index	IIa subgroup (n=21)	IIb subgroup (n=22)	Difference between groups (p)
Lymphocytes (g/l)	1.94±0.17	2.42±0.18	0.049
Lymphocytes (%)	36,.±2.1	42.3±2.6	0.089
T-lymphocytes (CD3+) (cells/µl)	971.0 (769.0-1352.0)	1245.0 (1007.0-1645.0)	*0.068
T-lymphocytes (CD3+) (%)	74.0 (68.0-80.0)	76.4 (67.0-83.0)	*0.697
T-helpers (CD4+) (cl/µl)	223.0 (145.0-417.0)	356.0 (229.0-488.0)	*0.174
T-helpers (CD4+) (%)	16.0 (12.0-24.0)	20.5 (15.0-26.2)	*0.519
B-lymphocytes (CD19+) (g/l)	0.16 (0.12-0.28)	0.12 (0.08-0.20)	*0.050
B-lymphocytes (CD19+) (%)	10.0 (8.60-10.50)	5.75 (4.10-8.50)	*0.017

Note. p - the level of significance of differences between subgroups according to the criteria of Student and Mann-Whitney (*)

It should be noted that the absolute and relative levels of B-lymphocytes also significantly differed between subgroups: in subgroup IIb the corresponding values were lower than in subgroup IIa - 0.12 (0.08-0.20) g/l and 5.75 (4.10-8.50) % against 0.16 (0.12-0.28) g/l at pU=0.050 and 10.0 (8.60-10.50)% at pU=0.017. This fact is confirmed by the inverse relationships of moderate force rs=-0.31 (p=0.050) and rs=-0.37 (p=0.015). That is, the average level of tetanus protection is clearly associated with normal absolute and relative levels of B-lymphocytes, as this group includes only 2 patients who received vaccination against tetanus in the last 5 years, in other words: completely eliminates the likelihood of interaction between B-lymphocytes and recent vaccination. It is the normal content of B-lymphocytes that indicates long-term protection against tetanus and is associated with longer immunological memory.

Discussion. Our study has shown the importance of studying antitoxic immunity against tetanus. Most patients did not receive routine vaccinations because they were not referred by medical professionals; immunoprophylaxis was performed only on emergency indications in some individuals. Therefore, strategies for the "maintenance and prevention therapy" of HIV-infected adults should be aimed at emphasizing the importance and necessity of vaccination. Moreover, the World Health Organization

(WHO), the British HIV Association (BHIVA), the European AIDS Clinical Society (EACS), the Centers for Disease Control and Prevention (CDC), the Advisory Committee on Immunization Practices (ACIP) and the current order of the Ministry of Health of Ukraine carrying out preventive vaccinations, do not deny carrying out immunization against tetanus to HIV-infected persons [6]. Thus, the WHO believes that tetanus toxoid is the safest for people with HIV [4]. There are several studies showing that there is no significant difference between the intensity of anti-tetanus immunity among HIV-infected and immunocompetent adults, although this may be due to a small sample: in the first study, the main group and controls were 15 [15], in the second 47 and 10 people, respectively [13]. In our study, it was found that the level of CD4+ -T-helpers and the level of viral load did not have a significant difference between groups with different antibody titers, which coincides with some studies [17]. Although there are many global studies where these indicators have direct or feedback, respectively [7, 12, 13, 18, 19]. An interesting fact was noted in our study that the intake of ART, as well as the duration of its receipt did not affect the protective values of the concentration of specific anti-tetanus antibodies.

In particular, adults and the elderly already have one or more major chronic diseases that are most vulnerable to infectious diseases for a number of reasons, namely age-related "immune age" - immunosenescence (progressive decline in immune function with age), reluctance to re-inject against diseases (diphtheria, tetanus, etc.). Thus, the level of vaccination coverage among the adult/elderly population is inconsistent or low. The main barriers to immunization include both patients and physicians who have negativeattitude towards vaccination and concerned about the side effects of vaccines. Unfortunately, in our country the legal and ethical basis of vaccine prevention is imperfect [20, 21, 22, 23]. Our study showed defects in vaccination - none of the patients received routine vaccination against tetanus, only after trauma (only 56.8% received post-exposure prophylaxis of tetanus among those who were injured).

Integrating lifelong vaccination is the best way to achieve the goal of maintaining the health and active longevity of adults with HIV.

Like the importance of ART, achieving a sustained immunological and virological response, tetanus vaccination should be an important component in ensuring the health and quality of life of HIV-infected adults.

Therefore, our study identified correlations between the leading clinical features of HIV-infected adults, which in a comprehensive assessment could indicate the presence/absence of the necessary immunological protection against tetanus.

Conclusions.

1. High risk of presence of low antibody levels against tetanus is associated significantly (from $p<0.05$ to $p<0.001$) with female sex (OR=2.69), the presence of anemia (OR=4.67), thrombocytopenia (OR=25.38), 2 or more opportunistic diseases (OR=3.62), including shingles (OR=4.88), hairy leukoplakia of the tongue (OR=7.72), frequent recurrences of VZV infection (OR=104.0) and simple herpes infection (OR=59.2), body weight deficit (OR=30.38), smoking (OR=7.13), low level of post-

exposure prophylaxis of tetanus with tetanus toxoid due to trauma with violation of the integrity of the skin (OR=58.1) and living in an urban area (OR=4.05).

2. The greatest protective opportunities regarding the increase of the level of anti-tetanus immunity in HIV-infected adults are respectively associated with the parenteral route of HIV infection (rs=0.20; p=0.06) and the receipt of IDUs substitution maintenance therapy (rs=0.34; p=0.081), the presence of no more than one opportunistic disease (rs=0.31; p=0.003), the absence of diseases of hairy leukoplakia of the tongue (rs=0.46; p<0.001) and shingles (rs=0.38; p<0.001), rare cases of recurrence of labial (rs=0.71; p<0.001) and shingles (rs=0.81; p<0.001), high coverage of post-exposure prophylaxis of tetanus with tetanus toxoid (rs=0.60) ; p<0,001), living in rural areas (rs=0.33; p<0.001), as well as smoking cessation (rs=0,44; p<0,001), normal laboratory blood counts (hemoglobin level - rs=0.41, p<0.001, platelets - rs=0.70; p<0.001) and body weight (rs=0.64; p<0.001).

3. A comprehensive assessment of these factors will allow, without conducting special studies, to identify risk groups that require vaccination against tetanus.

References:

1. Bonanni P, Bonaccorsi G, Lorini C, Santomauro F, Tiscione E, Boccalini S, et al. Focusing on the implementation of 21st century vaccines for adults. Vaccine. 2018;36(36):5358-65. doi: 10.1016/j.vaccine.2017.07.100.

2. Crum-Cianflone NF, Sullivan E. Vaccinations for the HIV-Infected Adult: A Review of the Current Recommendations, Part I. Infect Dis Ther. 2017;6(3):303-31. doi: 10.1007/s40121-017-0166-x

3. Doherty TM, Giudice GD, Maggi S. Adult vaccination as part of a healthy lifestyle: moving from medical intervention to health promotion. Annals of Medicine. 2019;51:2, 128-140, DOI: 10.1080/07853890.2019.1588470

4. Tetanus [Internet]. World Health Organitation. Available online: https://www.who.int/health-topics/tetanus/#tab=tab_3

5. Cunha GH, Galvao MT, Medeiros CM, Rocha RP, Lima MA, Fechine FV. Vaccination status of people living with HIV/AIDSin outpatient care in Fortaleza, Ceará, Brazil. Braz J Infect Dis. 2016;20(5):487-93. doi: 10.1016/j.bjid.2016.07.006

6. Revenko GO, Mavrutenkov VV. Immune response of adult people living with human immunodeficiency virus to the introduction of diphtheria and tetanus toxoid (review of literature). Actual Infectology. 2018;6(1): 7-11. [Ukranian]. DOI: 10.22141/2312-413x.6.1.2018.125629.

7. Dlamini SK, Madhi SA, Muloiwa R, von Gottberg A, Moosa MS, Meiring ST, at al. Guidelines for the vaccination of HIV-infected adolescents and adults in South Africa. Southern African Journal of HIV Medicine. 2018; 19(1):1-8. DOI: https://doi.org/10.4102/sajhivmed.v19i1.839

8. El Chaer F, El Sahly HM. Vaccination in the Adult Patient Infected with HIV: A Review of Vaccine Efficacy and Immunogenicity. Am J Med. 2019; 132(4):437-446.

doi: 10.1016/j.amjmed.2018.12.011.

9. Pinto Neto LFDS, Vieira JV, Ronchi NR. Vaccination coverage in a cohort of HIV-infected patients receiving care at an AIDS outpatient clinic in Espírito Santo, Brazil. Braz J Infect Dis. 2017;21(5):515-519. doi: 10.1016/j.bjid.2017.03.021.

10. Vicente-Alcalde N, Martín-Casquero T, Ruescas-Escolano E, Tuells J The Survivor: A Clinical Case of Tetanus in a Non-Immunized, Parenteral Drug User, Former Female Convict with HIV and HCV. Vaccines. 2020; 8(2): 308. doi:10.3390/vaccines8020308.

11. Public Health Center of the Ministry of Health of Ukraine [Internet]. Available online: https://phc.org.ua/kontrol-zakhvoryuvan/inshi-infekciyni-zakhvoryuvannya/monitoring-i-ocinka/infekciyna-zakhvoryuvanist-naselennya-ukraini

12. Grabmeier-Pfistershammer K, Herkner H, Touzeau-Roemer V, Rieger A, Burgmann H, Poeppl W. Low tetanus, diphtheria and acellular pertussis (Tdap) vaccination coverage among HIV infected individuals in Austria. Vaccine. 2015;.33(32):3929-3932. doi: 10.1016/j.vaccine.2015.06.056.

13. Mullaert J, Abgrall S, Lele N, Batteux F, Slama LB, Meritet JF, et al. Diphtheria, tetanus, poliomyelitis, yellow fever and hepatitis B seroprevalence among HIV1-infected migrants. Results from the ANRS VIHVO vaccine sub-study. Vaccine. 2015;33(38):4938-4944. doi: 10.1016/j.vaccine.2015.07.036.

14. Lang TA, Secic M. How to report statistics in medicine: Annotated Guidelines for Authors, Editors, and Reviewers. 2nd ed. Philadelphia: American College of physicians, 2006. 490p.

15. Salawu L, Ndakotsy MA. Tetanus antibody in Nigerians living with HIV/AIDS: A preliminary report. Malays J Microbiol.2010; 6(2): 111-114. doi: 10.21161/mjm.10708.

16. Fatokun MO, Enabor OO, Bello FA, Adesina OA, Arinola GO. Serum total IgG and tetanus specific IgG in Nigerian human immunodeficiency virus infected primigravidae the cord blood of their babies at birth. Ann Ib Postgrad Med. 2019;17(1):8-18.

17. Eslamifar A, Ramezani A, Banifazl M, Aghakhani A. Tetanus and diphtheria seroprevalence in patients infected with human immunodeficiency virus. A Iranian Journal of Pathology. 2012;7(1):27 – 31.

18. Sticchi L, Bruzzone B, Caligiuri P. Seroprevalence and vaccination coverage of vaccine-preventable diseases in perinatally HIV-1-infected patients. Hum Vaccin Immunother. 2015;11(1):263-9. doi: 10.4161/hv.36162

19. Andrade RM, Andrade AF, Lazaro MA, Vieira MM, Barros PO, Borner AR, et al. Failure of highly active antiretroviral therapy in reconstituting immune response to Clostridium tetani vaccine in aged AIDS patients. J Acquir Immune Defic Syndr. 2010; 54(1):10–17. doi: 10.1097/QAI.0b013e3181d6003b.

20. Revenko GO, Mavrutenkov VV. Clinical and pathogenetic significance of tetanus toxin. Clinical case. Child`s Healh. 2017; 12 (1): 92-95. [Ukranian]. DOI: 10.22141/2224-0551.12.1.2017.95032

21. Revenko HO, Mavrutenkov VV, Chykarenko ZO. Clinical and laboratory

predictors of antitoxic immunity against diphtheria and tetanus in adults with HIV infection. Medicni perspektivi. 2020;25(3):117-124. DOI:https://doi.org/10.26641/2307-0404.2020.3.214846.

22. Revenko HO. Strength of anti-diphtheria and anti-tetanus immunity in HIV-infected adults. Bulletin of problems biology and medicine. 2020; 158 (4):178-182 DOI:10.29254/2077-4214-2020-4-158-178-182.

23. Volokha A, Raus I, Donskoy B, Chernyshova L, Chernyshov V. Immunity against diphtheria and tetanus in HIV-infected children. Child Health. 2016;75 (7): 124-129. [Ukranian]. DOI: 10.22141/2224-0551.7.75.2016.86738