

**STRENGTH OF ANTI-DIPHTHERIA AND ANTI-TETANUS  
IMMUNITY IN HIV-INFECTED ADULTS**

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**Introduction.** At present, HIV-infected persons have a sufficient life expectancy that is close to the life expectancy of immunocompetent people due to antiretroviral therapy (ART). Thus, according to preliminary estimates, more than half of HIV-infected people in the USA and Europe will be over 60 years old by 2020. Availability of effective ART permitted to turn HIV infection from an acute and often fatal disease into a chronic latent infection, albeit rather complicated, but this gives doctors the opportunity to pay more attention to the needs of primary care for aging HIV-infected population [1,2].

Diphtheria and tetanus are potentially life-threatening infectious diseases that can only be prevented by routine immunization. Once one of these diseases starts, treatment options may be extremely limited [3,4,5], which is very relevant for our country. Therefore, the most effective strategy to combat these diseases is prevention, namely vaccination [6]. Under the immunodeficient conditions, in particular HIV infection, vaccination preventable infectious diseases have a more severe course compared to immunocompetent persons.

Analysis of literature sources has shown that there is no evidence to support the assumption of the negative impact of toxoids on the health condition of HIV-infected persons or on accelerating the progression of HIV infection [7].

Therefore, vaccination is definitely an important preventive strategy for HIV-positive people [8].

To date, there is no increased risk of side effects and reactions in HIV-infected persons to vaccination against diphtheria and tetanus [9,10,11,12,13]. The guidelines of the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), the Advisory Committee on Immunization Practices (ACIP), the European AIDS Clinical Society (EACS) and the British HIV Association (BHIVA) consider it necessary to immunize population with inactivated vaccines at any stage of HIV infection [5,7,9,10,11].

The presence of protective immunity after vaccination against diphtheria and tetanus is estimated by the level of antibodies against these pathogens [14].

Taking the above into account, it should be noted that studying the level of collective immunity among adults against infectious diseases, which are managed by means of vaccine prophylaxis, namely, diphtheria and tetanus, is not only relevant, but also refers to one of the fundamental fields in studying the population's health.

Today, the study of anti-toxic immunity against diphtheria and tetanus in HIV-infected adults is very limited

worldwide, and in Ukraine it is performed for the first time.

**The purpose of the work** is to estimate the state of post-vaccination immunity against diphtheria and tetanus by studying the seroprevalence of antibodies against these infections in HIV-infected adults.

**Object and methods.** The study was attended by 90 people living with HIV infection at the age of 22 to 60 years. The mean age was ( $M \pm m$ )  $40.1 \pm 0.9$  years ( $SD = 8.8$  years).

Observations of HIV-infected patients were carried out on the basis of the “Dnipropetrovsk prof. Y.G. Popkova City Clinical Hospital No. 21. “DRC”, City Center for Prevention and Control of HIV/AIDS in the city of Dnipro.

Copying of clinical and laboratory data was carried out from medical cards in the above-mentioned health care institutions.

Laboratory study of the levels of antidiphtheria and antitetanic antibodies in the observation group was carried out at the Diagnostic Center of SI “Dnipropetrovsk Medical Academy, MOH of Ukraine”. Diagnostic test systems RIDASCREEN Diphtheria IgG and RIDASCREEN Tetanus IgG (R-Biopharm AG, Germany) were used to estimate the immunity strengths to diphtheria and tetanus by means of immunoassay (ELISA). The examination was carried out in compliance with the manufacturer's instructions. The immunity status against diphtheria and tetanus was estimated by determining the concentration of antibodies in IU/ml. The assessment of the antidiphtheria immunity strengths was carried out according to the following criteria: up to 0.1 IU/ml – protection absent; 0.1-0.9 IU/ml – minimum level of protection; 1.0-1.4 IU/ml – moderate level of protection; 1.5 IU/ml and above is a high level of protection. Assessment of anti-tetanus immunity strengths was carried out as follows: up to 0.1 IU/ml – protection absent; 0.1-0.5 IU/ml – minimum level of protection; 0.6-1.0 IU/ml – moderate level of protection; 1.1 IU/ml and above – high level of protection.

Determination of HIV RNA in the blood was carried out using the polymerase chain reaction (PCR) method with real-time detection by the standardized technology with automated preparation. Determination of quantitative indices for lymphocyte subpopulations in peripheral blood was carried out by the flow cytometry method using monoclonal antibodies.

The control group involved 49 healthy immunocompetent volunteers from the corresponding age group (mean age  $39.0 \pm 1.2$  years). Copying of the serological monitoring results was carried out from the materials of the State Enterprise “Dnipropetrovsk Regional Laboratory Center, MOH of Ukraine”, based on the MOH of Ukraine Order No. 545 of 24.11.2003 “On the State of Ukraine's Population Immunization to Diphtheria and Tetanus”.

**Table 1 – Distribution of patients by age and gender**

Age groups	Gender				Total (n=90)	
	Men (n=39)		Women (n=51)			
	n	%	n	%	n	%
20-35 years	6	15.4	20	39.2	26	28.9
36-49 years	27	69.2	22	43.1	49	54.4
50-60 years	6	15.4	9	17.7	15	16.7

All the examined persons were fully acquainted with the scope of diagnostic measures and submitted the Informed Consent to participate in the scientific study carried out in compliance with bioethical standards.

Statistical processing of the results was performed using STATISTICA v.6.1 licensed software (Statsoft Inc., USA, Serial No. AGAR909E415822FA). Taking into account the law of quantitative data distribution, estimated by the Shapiro-Wilk test, parametric and non-parametric characteristics and methods of analysis were used: for the normal law, the arithmetic mean (M), the standard error (m), the standard deviation (SD), the Student's test (t), Fischer (F); in other cases – median (Me), interquartile scale (25% – 75%), Mann-Whitney (U), Kraskale-Wallis (H) criteria. Comparison of relative values was carried out according to the Pearson's chi-squared test ( $\chi^2$ ) criterion, including the Yates correction. The critical level of statistical significance (p) was taken to be <0.05.

**Results of the study and their discussion.** Among the observation group (n=90), the male population was 39 (43.3%), female – 51 (56.7%). Persons aged 36-49 were predominant (54.4%) (table 1). In anamnesis, nobody suffered from tetanus or diphtheria. With respect to the vaccination history: all persons received a course of vaccination against diphtheria and tetanus in childhood, namely 3 doses of vaccination and 3 doses of revaccination (the last at the age of 14 – according to previous national vaccination calendars). It should be noted that 25 persons (27.8%) underwent post-contact prophylaxis of tetanus due to trauma during the last 5 years.

The length of patients' hospital stay was on average  $5.22 \pm 0.40$  years. According to the way of HIV infection, the patients were distributed as follows: 63 (70.0%) had sexual transmission of the infection, which are currently dominating in the population of HIV-positive people and 27 (30.0%) – parenteral transmission among injecting drug users (IDUs). Among IDUs, 14 (51.9%) persons underwent substitution maintenance therapy (SMT) using methadone or buprenorphine. In clinical stages, patients with III-IV stages (according to the WHO clinical classification, 2006) dominated – 65 (72.2%), and clinical stages I-II were diagnosed in 25 (27.8%) of HIV-infected persons.

ART was administered to 69 patients (76.7%) and 21 (23.3%) did not receive treatment. The ART experience ranged from 1 to 11 years and averaged  $2.97 \pm 0.24$  years. ART regimens were distributed as follows: 50 (72.5%) patients received the scheme of 2 nucleoside and 1 non-nucleoside reverse transcriptase inhibitors and 19 (27.5%) – 2 nucleoside reverse transcriptase inhibitors and 1 protease inhibitor (table 2).

ART was prescribed immediately after the diagnosis of HIV infection to 29 (42.0%) patients, within 1-3 years – to 19 (27.6%) and 4 or more years after diagnosis – to 21 (30.4%) persons. High preference to ART was ob-

served in 48 (69.6%) patients compared to 21 (30.4%) with low preference.

**Table 2 – ART regimens received by HIV-infected persons**

Scheme	Number of patients (n=69)	
	n	%
TDF/FTC+EFV	20	29.0
AZT/3TC+EFV	14	20.3
TDF/FTC+LPV/r	10	14.5
TDF/3TC+EFV	8	11.5
TDF/3TC+LPV/r	7	10.1
ABC/3TC+EFV	5	7.2
TDF/FTC+NVP	2	2.9
TDF/3TC+LPV/r	1	1.5
TDF/3TC+NVP	1	1.5
ABC/3TC+LPV/r	1	1.5

Opportunistic infectious diseases were registered in all patients and comprised herpes zoster (54.4%), oropharyngeal candidiasis (36.7%), pulmonary tuberculosis (34.4%) and herpes labialis (33.3%) (table 3). Moreover, 44 (48.9%) persons had one disease, 46 (51.1%) persons had two and more. Thus, among the cohort of patients with tuberculous lung disease (n = 31), focal and infiltrative forms of tuberculosis were diagnosed in 11 (35.5%) persons, and disseminated form – in 20 (64.5%) patients. Among 30 patients with manifest infections caused by herpes simplex virus, in 20 (67.7%) cases, relapses were observed at most once a year and in 10 (33.3%) patients – repeated cases were recorded twice and more a year. In 49 patients with relapsed VZV infection, the herpes zoster's relapse was observed more than once a year in 34 (69.4%) cases versus 15 (30.6%), when repeated episodes of the disease were diagnosed less frequently than once a year.

**Table 3 – Frequency of opportunistic infections in HIV-infected individuals**

Disease	Number of patients (n=69)	
	n	%
Herpes labialis	30	33.3
Herpes zoster	49	54.4
Oropharyngeal candidiasis	33	36.7
Onychomycosis	4	4.4
Pulmonary tuberculosis	31	34.4
Cerebral toxoplasmosis	3	3.3
Pneumocystic pneumonia	2	2.2

The mean CD4<sup>+</sup> T-lymphocytes level made  $376.2 \pm 26.4$  (range: 16-1230) cl/ $\mu$ l. The viral load of HIV RNA ranged from 40 cop/ $\mu$ l to 564457 cop/ $\mu$ l, the median was 40 (240-283) cop/ $\mu$ l.

Our study identified significant differences between the titres of anti-toxic antibodies in HIV-infected and immunocompetent adults.

It was established that the median of antiphtheria antibodies in the main group was 0.17 (0.09–0.38) IU/ml, which is by 6,1 times lower than the same index in the control group – 1.03 (0.56–1.27) IU/ml (p<0.001 by Mann-Whitney U-criteria) (fig. 1A).

A similar situation was observed with anti-tetanus antibodies: the median was 0.59 (0.28–1.09) IU/ml in

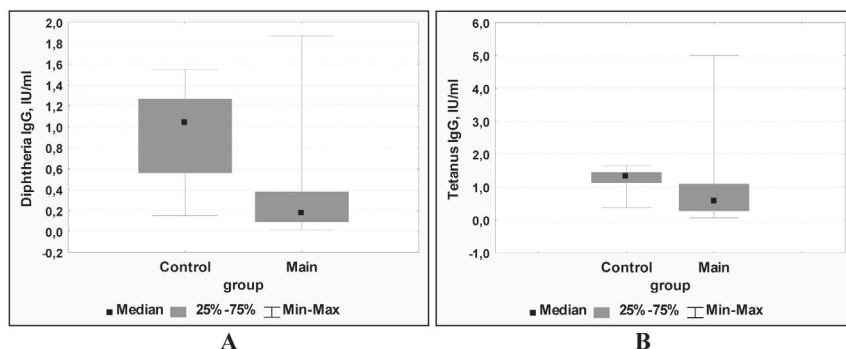


Figure 1 – Levels of anti-diphtheria (A) and anti-tetanus (B) antibodies in HIV-infected persons and in the control group.

HIV-positive persons, which is by 2.3 times lower than in the control group – 1,33 (1,13–1,45) IU/ml ( $p < 0.001$  by the U-criterion) (fig. 1B).

The more detailed study of the anti-toxicity immunity indices revealed that the percentage of persons protected against diphtheria in the main group (medium and high titers) was 6.6% ( $n=6$ ) and is considered to be critically low, which is probably less than in the control group – 59.2% ( $n=29$ ) ( $p < 0.001$  for  $\chi^2$ ).

The minimum level of protection was observed in 60.0% ( $n=54$ ) of the surveyed HIV-infected individuals, which is highly questionable in terms of protection against diphtheria, as opposed to immunocompetent persons – 40.8% ( $n=20$ ) ( $p=0.030$  per  $\chi^2$ ). In 33.3% ( $n=30$ ) of the observed HIV-infected patients, the titer of antibodies below 0.1 IU/ml was found, which corresponds to the seronegative status, in contrast to the control group, where such titers were not registered ( $p < 0.001$  for  $\chi^2$ ). In other words, the unprotected against diphtheria layer of patients in the main group was 93.3% ( $n=84$ ) versus 40.8% ( $n=20$ ) ( $p < 0.001$  for  $\chi^2$ ) (table 4).

A similar situation was observed with seroprevalence of anti-tetanus antibodies. Thus, the percentage of HIV-infected persons with medium and high titer of anti-tetanus antibodies is also quite low and made 47.8% ( $n=43$ ), which is believed to be lower than that in the control group – 91.8% ( $n=45$ ) ( $p < 0,001$  for  $\chi^2$ ). That is, only the control group is approaching the required level of tetanus vaccination coverage – 95%, which reflects the adequacy of mass vaccination (since there is

no post-infection immunity against tetanus) among adults against this infectious disease. The unprotected cohort of HIV-infected persons, namely: seronegative and those with the minimum level of protection, reached 52.2% ( $n=47$ ), compared to 8.2% ( $n=4$ ) of immunocompetent persons ( $p < 0.001$  for  $\chi^2$ ).

We did not find any reliable correlations between the levels of antitoxic antibodies against diphtheria and tetanus and the number

Table 4 – Distribution of persons depending on the antitoxic immunity strength

Immunity	Antibodies titers (IU/ml)	Main group (n=90)		Control group (n=49)		Difference between the groups (p)
		n	%	n	%	
Against diphtheria	< 0.1	30	33.3	0	0	<0.001*
	0.1 – 0.9	54	60.0	20	40.8	0.030
	1.0 – 1.4	3	3.3	27	55.1	<0.001
	≥ 1.5	3	3.3	2	4.1	0.802*
Against tetanus	< 0.1	12	13.3	0	0	0.018*
	0.1 – 0.5	35	38.9	4	8.2	<0.001*
	0.6 – 1.0	21	23.3	3	6.1	0.020*
	> 1.0	22	24.5	42	85.7	<0.001

Note: the significance level of the differences between the groups (p) is calculated by  $\chi^2$  criterion, including the Yates correction (\*).

of CD4<sup>+</sup> T-lymphocytes in the patients of the main group, as evidenced by the data in figure 2.

Thus, the mean anti-diphtheria antibody levels ranged from 0.21 (0.10–0.41) IU/ml at a concentration of CD4<sup>+</sup> T-lymphocytes below 200 cells/ $\mu$ l ( $n=25$ ; 27.8%) to 0.17 (0.07-0.38) IU/ml and 0.14 (0.09-0.34) at levels of CD4<sup>+</sup> cells 200-500 cells/ $\mu$ l ( $n=42$ ; 46.7%) and above 500 cells/ $\mu$ l ( $n=23$ ; 25.5%), respectively (according to the Kruskal-Wallis  $H=0.917$ ;  $p=0.632$ ). The mean titers of anti-tetanus antibodies with the corresponding grades of CD4<sup>+</sup> T-lymphocytes in HIV-infected persons were: 0.79 (0.31-1.08) IU/ml, 0.64 (0.25-1.50) IU/ml and 0.42 (0.15-1.09) IU/ml ( $H=0.476$ ;  $p=0.788$ ).

Consequently, the intensity of post-vaccine immunity against the studied infectious diseases in HIV-infected adults is significantly lower in comparison with immunocompetent persons, which is probably due to the fact that diphtheria and tetanus toxoids belongs to vaccines generating T-cell-dependent response (“T-cell-dependent response”) and the duration of the immune response depends on the state of the T-cell component [15].

This fact permits to consider the post-vaccine immunity strengths against diphtheria and tetanus as one of the additional indicators of immunosuppression.

Finally, the presence of a large pool of “susceptible to diphtheria” among both HIV-infected persons – 93.3% ( $n=84$ ) and among immunocompetent ones – 40.8% ( $n=20$ ), indicates the risk of diphtheria

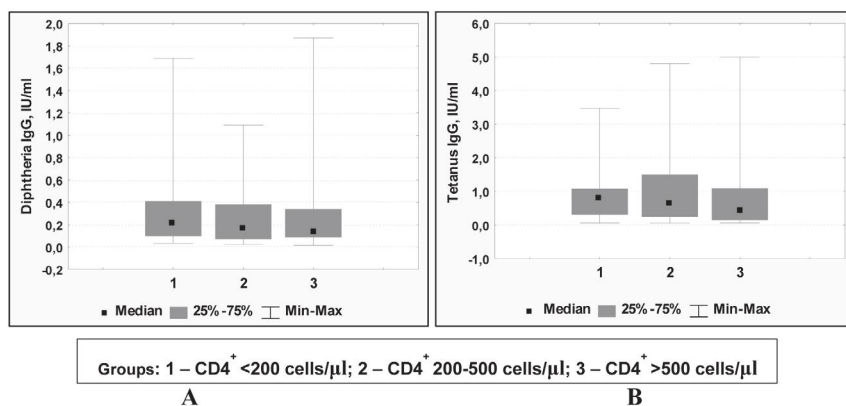


Figure 2 – Titres of antitoxic antibodies against diphtheria (A) and tetanus (B) depending on the immunosuppression degree.

epidemic occurrence, where the only means of prevention is immediate vaccination of the adult population in Ukraine.

### Conclusions

1. Any adult HIV-infected person did not receive a planned vaccination against diphtheria and tetanus in adulthood. Post-contact prophylaxis of tetanus in connection with injuries took place in 25 (27.8%) cases.

2. The seroprevalence level of HIV-infected persons against diphtheria and tetanus is significantly lower than that of immunocompetent ones – a significant number of HIV-positive adults do not have sufficient antibody

titers, namely: against diphtheria – 93.3% (n=84) and against tetanus – 52.2% (n=47).

3. Presence of a large group of people “susceptible to diphtheria”, both among HIV-infected persons and among immunocompetent ones, indicates the risk of diphtheria epidemic and requires an immediate vaccination of the adult population in Ukraine.

**Prospects of further research** should be aimed at identifying clinical and laboratory predictors of the strength of antitoxic immunity against diphtheria and tetanus in HIV-infected adults, which can further serve as important indicators for further development of a “vaccination roadmap” for HIV-infected patients.

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### НАПРУЖЕНІСТЬ ПРОТИДИФТЕРІЙНОГО ТА ПРОТИПРАВЦЕВОГО ІМУНІТЕТУ У ВІЛ-ІНФІКОВАНИХ ДОРΟΣЛИХ ОСІБ

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**Резюме.** Ефективна антиретровірусна терапія призвела до того, що ВІЛ-інфекція стала керованою хворобою, тому стає актуальне питання про імунізацію інфекційних захворювань серед цих пацієнтів. Дифтерія та правець можна запобігти лише вакцинацією. *Мета дослідження:* оцінити стан поствакцинального імунітету проти дифтерії та правця шляхом дослідження серопревалентності антитіл щодо цих інфекцій у ВІЛ-інфікованих дорослих осіб. *Об'єкт і методи:* обстежено 90 ВІЛ-інфікованих пацієнтів віком від 22 до 60 років (основна група). Групу контролю становили 49 імунізаційних добровольців відповідного віку. Визначення рівнів протидифтерійних та протиправцевих антитіл проводилось методом ІФА з використанням діагностичних тест-систем RIDASCREEN Diphtheria IgG та RIDASCREEN Tetanus IgG (R-Biopharm AG, Germany). Статистичну обробку проводили за допомогою ліцензійного програмного продукту STATISTICA v.6.1. *Результати дослідження.* Визначені суттєві розбіжності між титрами антитоксичних антитіл у ВІЛ-інфікованих та імунізаційних дорослих осіб. Медіана протидифтерійних антитіл у ВІЛ-позитивних осіб становила 0,17 (0,09-0,38) МО/мл, що у 6,1 рази нижче ніж у контрольній групі – 1,03 (0,56-1,27) МО/мл (p<0,001 за критерієм Манна-Уїтні). Медіана протиправцевих антитіл у основній групі дорівнювала 0,59 (0,28-1,09) МО/мл, що у 2,3 рази менше показника у контрольній групі – 1,33 (1,13-1,45) МО/мл (p<0,001). Незахищений прошарок проти дифтерії серед осіб основної групи становив 93,3% (n=84), проти правця – 52,2% (n=47). Не виявлено вірогідних зв'язків між рівнями антитоксичних антитіл проти дифтерії і правця та кількістю CD4<sup>+</sup> Т-лімфоцитів у ВІЛ-інфікованих осіб.

**Висновки.** ВІЛ-інфіковані особи дорослого віку є групою ризику щодо потенційного захворювання на дифтерію та правець, оскільки мають низький специфічний імунітет. Це націлює на обов'язковість їх вакцинації проти зазначених інфекційних захворювань.

**Ключові слова:** ВІЛ-інфекція, вакцинація, імунітет, серопревалентність, дифтерія, правець.

### НАПРЯЖЕННОСТЬ ПРОТИВОДИФТЕРИЙНОГО И ПРОТИВОСТОЛБНЯЧНОГО ИММУНИТЕТА У ВИЧ-ИНФИЦИРОВАННЫХ ВЗРОСЛЫХ ЛЮДЕЙ

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**Резюме.** Эффективная антиретровирусная терапия привела к тому, что ВИЧ-инфекция стала управляемой болезнью, поэтому ставится актуальный вопрос об иммунопрофилактике инфекционных заболеваний среди этих пациентов. Дифтерию и столбняк можно предотвратить только вакцинацией. *Цель исследования:* оценить состояние поствакцинального иммунитета против дифтерии и столбняка путем исследования серопревалентности антител к этим инфекциям у ВИЧ-инфицированных взрослых людей. *Объект и методы:* обследовано 90 ВИЧ-инфицированных пациентов в возрасте от 22 до 60 лет (основная группа). Группу контроля составили 49 иммунокомпетентных добровольцев соответствующего возраста. Определение уровней противодифтерийных и противостолбнячных антител проводилось методом ИФА с использованием диагностических тест-систем RIDASCREEN Diphtheria IgG и RIDASCREEN Tetanus IgG (R-Biopharm AG, Germany). Статистическую обработку проводили с помощью лицензионного программного продукта STATISTICA v.6.1. *Результаты исследования.* Выявлены существенные расхождения между титрами антитоксических антител у ВИЧ-инфицированных и иммунокомпетентных взрослых людей. Медиана противодифтерийных антител у ВИЧ-позитивных лиц составила 0,17 (0,09-0,38) МЕ/мл, что в 6,1 раз ниже чем в контрольной группе – 1,03 (0,56-1,27) МО/мл ( $p < 0,001$  по критерию Манна-Уитни). Медиана противостолбнячных антител в основной группе равнялась 0,59 (0,28-1,09) МЕ/мл, в 2,3 раза меньше показателя в контрольной группе – 1,33 (1,13-1,45) МЕ/мл ( $p < 0,001$ ). Незащищенная когорта против дифтерии среди лиц основной группы составила 93,3% ( $n=84$ ), против столбняка – 52,2% ( $n=47$ ). Не выявлено достоверных связей между уровнями антитоксических антител против дифтерии и столбняка и количеством CD4<sup>+</sup> Т-лимфоцитов у ВИЧ-инфицированных лиц.

*Выводы.* ВИЧ-инфицированные лица взрослого возраста являются группой риска в отношении потенциального заболевания дифтерией и столбняком, поскольку имеют низкий специфический иммунитет. Это нацеливает на обязательность их вакцинации против указанных инфекционных заболеваний.

**Ключевые слова:** ВИЧ-инфекция, вакцинация, иммунитет, серопревалентность, дифтерия, столбняк.

### STRENGTH OF ANTI-DIPHTHERIA AND ANTI-TETANUS IMMUNITY IN HIV-INFECTED ADULTS

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**Abstract.** Effective antiretroviral therapy has transformed HIV into a manageable disease, therefore the issue of immunological prophylaxis of infectious diseases among these patients arises. Diphtheria and tetanus can only be prevented by vaccination. *The purpose of the study* was to assess the status of post-vaccination immunity against diphtheria and tetanus by investigating the seroprevalence of antibodies against these infections in HIV-infected adults. The total of 90 HIV-infected patients aged 22 to 60 years were examined (main group). The control group consisted of 49 immunocompetent volunteers of the corresponding age. Determination of the anti-diphtheria and anti-tetanus antibodies levels was carried out by means of immunoassay analysis using RIDASCREEN Diphtheria IgG and RIDASCREEN Tetanus IgG (R-Biopharm AG, Germany) diagnostic test systems. Statistical processing was performed using the STATISTICA v.6.1 licensed software. Significant differences were found between the titers of anti-toxic antibodies in HIV-infected and immunocompetent adults. The median of antidiphtherial antibodies in HIV-positive individuals was 0.17 (0.09-0.38) IU/ml, which is by 6.1 times lower than that in the control group – 1.03 (0.56-1.27) IU/ml ( $p < 0.001$  by the Mann-Whitney criterion). The median of anti-tetanus antibodies in the main group was 0.59 (0.28-1.09) IU/ml, which is by 2.3 times less than that in the control group – 1.33 (1.13-1.45) IU/ml ( $p < 0.001$ ). The population unprotected against diphtheria among the main group was 93.3% ( $n=84$ ), against tetanus – 52.2% ( $n=47$ ). There was no reliable association between the levels of antitoxic antibodies against diphtheria and tetanus and the number of CD4<sup>+</sup> T-lymphocytes in HIV-infected individuals. HIV-positive adults constitute a risk group for potential diphtheria and tetanus as they have low specific immunity. It justifies their mandatory vaccination against these infectious diseases.

**Key words:** HIV infection, vaccination, immunity, seroprevalence, diphtheria, tetanus.

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