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Diagnostic and genetic markers associated with pulmonary tuberculosis in HIV-infected individuals

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Abstract

An important aspect of monitoring, further timely and effective treatment of HIV-TB coinfection is timely and correct diagnosis based on comprehensive clinical, laboratory and instrumental studies. Many factors play a role in the development of tuberculosis in HIV-infected people, but the key and quite important elements are the study of genetic markers and biomarkers of inflammation. A number of studies have been carried out on inflammatory markers, but IL-6, INF-γ, MIG, CRP, IL-18 remain relevant and insufficiently studied in coinfection. A comprehensive study of them will be important in the screening of HIV-TB coinfection). Determining the presence of (SNP) rs4331426 located in chromosome 18q11.2 in HIV-infected and AIDS patients will solve the issue of predisposition to the development of tuberculosis in the early stages of HIV infection and contribute to the development of further tactics of patients treatment and management.

Keywords: HIV infection; tuberculosis; coinfection; biomarkers of inflammation; genetic markers, diagnosis.

Introduction. An urgent problem of society is the growing incidence of HIV infection and the development of HIV-infected opportunistic infections, including pulmonary tuberculosis. The probability of developing the active form of tuberculosis in HIV-infected people is 18 (15-21) times higher than the same rate among uninfected people. HIV-tuberculosis coinfection is a fatal combination and leads to deterioration of the patient's condition, and subsequently to death. About 208,000 people died from HIV-associated tuberculosis in 2019. In 2019, the proportion of registered TB patients with documented HIV was 69%, up from 64% in 2018. According to the WHO, about 86% of patients with HIV-associated tuberculosis are in the African region. In total, 88% of patients with HIV-TB coinfection received antiretroviral therapy (ART) in 2019 [1**].**

The incidence of tuberculosis among HIV-infected people in Ukraine was 4398.0 in 2019 (10.5 people per 100,000 population), including active pulmonary tuberculosis amounted to 3374.0 (8.0 per 100,000 population). In Sumy oblast, the figures were 53.0 and 4.9 per 100,000 population respectively, including 47.0 and 4.4 with active pulmonary tuberculosis per 100,000 population. **[**2**].**

A comprehensive approach is needed, which will include, first of all, the appointment of ART for HIV-infected patients and timely, rapid diagnosis of opportunistic infections, including active pulmonary tuberculosis to address the problem of HIV-TB coinfection.

HIV-TB coinfection can occur in two variants: latent tuberculosis infection (LTBI) and manifest form, which is characterized by damage to various organs and systems. LTBI is a stable immune response to the presence of Mycobacterium tuberculosis in the body without clinical signs of the active form of tuberculosis **[**3**].** A tuberculin skin test and a quantiferon test (QFT) are performed to diagnose LTBI. To recognize the active form of tuberculosis it is necessary to detect clinical symptoms, perform radiography or CT scan, culturological method of identification of Mycobacterium tuberculosis, GeneXpert MBT / RIF, nucleic acid amplification (PCR), LF-LAM **[**4**].** These studies do not answer whether a patient in the early stages of HIV infection is prone to infection and progression of opportunistic infection. In order to determine the predisposition to the development of tuberculosis infection in HIV-infected people, a large number of studies were conducted: the effect of C-reactive protein on the development of TB **[**5**]**; the importance of vitamin A and D deficiency, which may be a predictor of tuberculosis in people living with HIV (PLHIV) **[**6**]**. One of the most progressive

and the most recent areas of research is the study of the relationship of the genome with the development of tuberculosis in the human population **[**7-9**]**. In this regard, a promising direction is the study of the peculiarities of genetic polymorphism of the tuberculosis genome in chromosomes associated with the HIV-positive status of a person..

Purpose. To analyze current research to determine effective diagnostic markers associated with the development of tuberculosis in HIV-infected people, their interconnection and the possibility of further use in diagnosis.

Materials and methods. Statistical data of the Center for Medical Statistics, the Center for Public Health, data from the World Health Organization, theoretical material, analysis of the latest world research and clinical results obtained in the original articles recorded in the scientific databases Scopus and Web of Science.

Review. Mycobacterium tuberculosis potentiates the increase in HIV-1 replication, especially in the inflammatory focus. Broncho-alveolar lavage fluid of inflammatory cells of the lungs contains elevated levels of p24 HIV-1, compared with unaffected areas. Mycobacterium tuberculosis activates the immune system, which is observed in people with coinfection and leads to accelerated development of AIDS and an increased risk of concomitant opportunistic infection and death. Lack of accurate diagnosis of TB and reliable biomarkers for monitoring LTBI and active tuberculosis in HIV-1 coinfection leads to an unfavorable prognosis for PLHIV **[10]**.

The need to diagnose tuberculosis, which can be asymptomatic (LTBI) and manifest, in particular tuberculosis with Mycobacterium tuberculosis, is paramount in establishing HIV-positive status..

A skin allergy test is used to diagnose LTBI. But this method is not reliable as it depends on many factors: an allergic reaction to the components of tuberculin, the development of a false positive response to worm infestation, etc. **[11]**. It is also possible to use C-tb skin test. This test is based on Mycobacterium tuberculosis - specific RD1 antigens ESAT-6 and CFP10, which are used in the analysis of interferon release (IGRA). C-Tb combines the mechanism of a skin test without the need for laboratory processing and high specificity, due to the use of M. tuberculosis-specific antigens, which are not present in the tuberculosis vaccine (BCG) or most mycobacteria common in the environment. Therefore, this test, along with others, can be used to diagnose LTBI **[**12, 13**]**.

Gamma-interferon release analysis (IGRA) is also often used in screening. IGRA includes QuantiFERON-TB Gold Plus (Cellestis, Australia) and the T-SPOT test (Oxford Immunotec, UK) **[**14**]**. The QuantiFERON test has recently been used in Ukraine to diagnose

LTBI. The principle of its action is to detect in vitro production of gamma-interferon by patient's sensitized T-lymphocytes, which are stimulated in vitro by specific proteins that are part of the complex of Mycobacterium tuberculosis - ESAT-6 and CFP-1. These antigens are characteristic of the complex of Mycobacterium tuberculosis: M. tuberculosis, M. bovis, M. Africanum; as well as for non-tuberculous mycobacteria: M. kansasii, M. szulgai and M. marinum. Interpretation of results: negative CFT - LTI is unlikely; positive - LTI is very likely; indeterminate - means that the patient's immune system is weakened. The probability of obtaining false-negative results in HIV-infected people increases with a decrease in the number of CD4 + cells less than 200 cells / μl **[**15, 16**].**

A comparative study of the use of QuantiFERON-TB Gold Plus in the presence of HIV infection and negative status was conducted to interpret the impact of HIV on the results of this test. According to the obtained results, positive HIV status does not affect the test results in active tuberculosis, while in LTBI there are uncertain results. **[**17**].**

Quantiferon Gold Plus test can be used to determine specific biomarkers of tuberculosis activity. A large number of host biomarkers found in unstimulated supernatants have shown high efficiency in diagnosis. Among these markers there are the following - ITAC-1, IL-3, I-309 and MIG, EGF, TGF-α, IL-2, IL-33, Apo-A1, ADAMTS13, GM-CSF and IP-10, which can be markers of pulmonary and extrapulmonary active tuberculous process in the future **[**18**].**

IGRA LIOFeron®TB / LTBI also can be used **[**19**]**. In 2019, Lionex GmbH (Braunschweig, Germany) introduced a new IGRA test called LIOFeron®TB / LTBI, which for the first time contains alanine dehydrogenase (Ala-DH) Mycobacterium tuberculosis (owned by Lionex). This antigen does not produce BCG, and it is known that T epitopes of CD8 + lymphocytes, limited by the main histocompatibility complex of class I, are present in Ala-DH. Another property of this antigen is that it is involved in the adaptation of Mycobacterium tuberculosis to the anaerobic resting stage in LTBI. It has recently become known that the determination of the concentration of IL-2, Ala-DH can be used to differentiate active tuberculosis from LTBI **[**20**]**. Compared to TST, IGRA positivity is consistent with the risk of TB infection and is probably the best way to diagnose LTBI in HIV-infected patients. **[**21**]**

Analytical comparative studies of tests for the LTBI diagnosis were conducted to determine the most effective method. TST QuantiFERON-TB Gold in Tube (QFTGT), T-SPOT.TB, IGRA were included in the comparative sample. They were involved in a comparative sample TST QuantiFERON-TB Gold in Tube (QFTGT), T-SPOT.TB, IGRA.

TST QuantiFERON-TB Gold in Tube (QFTGT), T-SPOT.TB, IGRA were included in the comparative sample. The tests for conformity and difference in proportions were evaluated, and the variability of the research methodology was also determined. At detection of LTBI almost identical reactivity of the quantiferon test and skin test, in the conditions of low prevalence of tuberculosis is noted. In the active form of tuberculosis, a slightly higher reactivity of IGRA or T-SPOT.TB was detected than the skin allergy test. **[**22**].**

HIV-tuberculosis coinfection currently has a malignant course in Ukraine, which is probably due to low culture of the population, insufficient level of medical care, underfunding of the medical sector and distrust of the population to health workers, which leads to negative prognostic consequences. Most often in this group of patients there is pulmonary tuberculosis, which at the level of CD4 cells more than 200 cells / μl is characterized by infiltrative changes in the apex of the lungs and the possible formation of cavities; when the level of CD4 cells is less than 200 cells / μl, the disease is of the type of primary tuberculosis with negative test results for the causative agent of tuberculosis, with a further decrease in T lymphocytes in the blood there are non-cavernous atypical changes in the lungs **[**23**].**

Microbiological studies for the diagnosis of tuberculosis have not lost their relevance and effectiveness at this time, even in the context of the development of HIV-tuberculosis coinfection. In 1977, it was developed a method for radiometric detection of the growth of mycobacteria in a selective liquid medium, which gave impetus to the creation of the most common and available systems of broth cultivation: BACTEC 460 (BD), BBL Septi-Chek AFB (BD), BBL MGIT (BD), BACTEC MGIT 960 (BD), MB / BacT (Organon Teknika) and Bast / Alert 3D (BioMerioux). Among the molecular genetic diagnostic methods, DNA strip technology and GeneXpert have become widely used. The test is designed to examine samples from patients who have clinical signs of pulmonary tuberculosis and is a mandatory method for determining the active form of pulmonary tuberculosis in HIV-infected individuals **[**24**].**

Among the HIV-positive cohort of people it was mainly detected the pulmonary tuberculosis. Infiltrative and disseminated forms were the most common in clinical forms. Most patients with TB-HIV coinfection have severe immunodeficiency, the number of CD4 + cells is less than 200 cells / μl. In the lungs affected by tuberculosis in combination with HIV, bilateral localization of the process, destructive changes and bacterial excretion were more often detected. Radiological changes in tuberculosis in HIV-positive patients were atypical mid- and lower-part localization and involvement of the lymphatic system [25**].**

In a diverse cohort of HIV-infected adults from predominantly low- and middle-income countries, vitamin A and D deficiency at the onset of ART was independently associated with an increased risk of developing TB infection over the next two years. Vitamins A and D can be important modifiers of tuberculosis risk in HIV-infected high-risk patients, in patients at the beginning of ART in conditions of insufficient resources in highly endemic tuberculosis regions. In vitro studies have demonstrated the ability of vitamin A to inhibit the replication of Mycobacterium tuberculosis in culture and within macrophages. Vitamin D modulates innate immunity and adaptive immune response - it helps to suppress Th1 immune responses, but also promotes activation of macrophages mediated by Toll-like receptors, maturation of cathelicidin-dependent phagosomes and fusion with lysosomes, as well as intracellular destruction of Mycobacterium tuberculosis **[**26**].**

One of the ways to improve the diagnostic and prognostic characteristics of HIV-TB coinfection is the introduction of determination the level of CRP, as an additional research method to tuberculosis screening. The examination was scheduled before the start of diagnosis by standard methods and before the start of ART. Elevated CRP levels were found, which correlated with confirmation of HIV coinfection with tuberculosis **[**27**].**

LF-LAM (lipoarabinomannan) is also used to diagnose tuberculosis in HIV-infected people. LAM is a component of the cell wall of mycobacteria, which after its destruction in the kidneys enters the urine. Immunochromatographic method is developed specifically for patients with severe immunosuppression. Among the 6 examined patients with severe disease in the hospital, 4 had a positive LF-LAM test and this confirmed the presence of tuberculosis. In Ukraine, this test may be an additional method for diagnosing of tuberculosis in HIV-infected people **[**28**].** The LF-LAM test can also be used in individuals with an unknown number of T lymphocytes **[**29**].**

Genetic indicators can be used for the prognostic purpose of tuberculosis in HIV-infected patients. The presence of single nucleotide polymorphisms in certain loci of chromosomes may indicate a predisposition to the development of tuberculosis in some populations. Thus, among the cohort of Taiwanese in the framework of full-genome associative studies on single nucleotide polymorphism (SNP) rs4331426, located in the gene-poor region of chromosome 18q11.2, a study was conducted on the predisposition to the development of tuberculosis. According to the results, it was found a link with this polymorphism, especially in women **[**30**].**

Direct measurement of unstimulated plasma cytokines / chemokines in peripheral blood is a promising approach to tuberculosis screening. Panels of inflammatory biomarkers

retained high sensitivity to negative smear tuberculosis and achieved improved specificity compared to individual cytokines / chemokines. These markers should be further evaluated in an outpatient setting, where a greater proportion of TB screening is performed and when there are other diseases associated with systemic inflammation that are less common. The following inflammatory markers were used in the study: IL-6, INF-γ, MIG, CRP, IL-18. Biomarker panels are of greater diagnostic value than each biomarker alone **[**31**].**

Conclusions

In Ukraine, as in the rest of the world, it is important to address the issues related to pulmonary tuberculosis in HIV-infected people, which is diagnosed late and is life-threatening for these patients and others. HIV-TB coinfection is predominantly latent, due to the severity of the immunodeficiency, with the infection developing asymptomatically.

One of the promising areas for studying the development of tuberculosis in HIV-infected people is the study of inflammatory markers IL-6, INF-γ, MIG, CRP, IL-18, which will improve the screening of tuberculosis when the patient seeks the primary care and will provide the correct adjustment of its further diagnostic and treatment plan.

Equally interesting is the study of chromosome genome polymorphism, which may serve to prevent the development of tuberculosis in the early detection of HIV infection in the future. Prior to that, no one in the world or in Ukraine had studied the genome associated with the development of pulmonary tuberculosis in HIV-infected chromosome 18q11.2. This study will develop a further strategy for diagnosis and treatment.

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