

Features of the Clinical Course, the State of Diagnosis and Treatment of Hiv-Associated Pulmonary Tuberculosis in Modern Conditions Literature Review

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ABSTRACT

The article reviews the scientific works of 108 sources, of which 87(80,6%) - scientific works belong to authors from the CIS countries, and 21 (19,4%) - from far abroad. The results of the analysis showed that there is enough literature devoted to solving the complex problem of HIV-associated pulmonary tuberculosis, but the rapidly progressing severe complication of an accompanying lethal outcome requires the search for new methods of diagnosis and treatment.

KEY WORDS: HIV-associated pulmonary tuberculosis, diagnosis, treatment, prognosis.

INTRODUCTION

Tuberculosis (TB) is one of the main causes of death of HIV-infected people and belongs to the AIDS indicator diseases. So, in 2016, the share of tuberculosis was 40% in the structure of deaths among HIV-positive patients in the world. The risk of developing tuberculosis in HIV-infected people is 20-30 times higher than in uninfected people [5,7,20].

HIV-associated tuberculosis is becoming one of the main problems of modern phthisiology. Over the past decade, there has been a manifold increase in the number of cases of the disease and high mortality rates among patients of both medical institutions of the state health care system and penitentiary institutions [23]. In the Russian Federation, more than one in five (in institutions of the penal system - more than one in three) newly diagnosed TB patient is HIV-infected [21,23].

In recent years, there has been a significant increase in the spread of the combination of tuberculosis and HIV infection [5]. The progression of HIV infection often leads to the development of tuberculosis among persons previously infected with mycobacterium tuberculosis.

Epidemiological features. The current epidemic situation is characterized by a constant increase in the number of patients with HIV infection [83.96]. This is due to both the registration of new cases of the disease and the prolongation of the life of patients as a result of the widespread use

of antiretroviral therapy (ART) [8,16]. The steady progression of HIV infection is accompanied by the addition of secondary diseases, which often determine the life expectancy of patients. One of the most common secondary diseases is tuberculosis; the risk of developing tuberculosis in HIV-infected patients is 20-37 times higher than in HIV-negative individuals [67,91].

A significant and widely discussed problem is the growing progression of the HIV epidemic, characterized by an increase in the number of new cases, high levels of incidence and mortality of the population. The current epidemic situation contributes to the activation of the development of mixed forms of these socially significant infectious diseases, which, in turn, can have a significant impact on the negative manifestations of their epidemic processes, especially in areas of high risk of both infections [82,85,86].

In recent decades, HIV infection has had a significant impact on the spread of tuberculosis in the world. Indicators of morbidity, mortality, and the effectiveness of treatment of patients with tuberculosis are largely associated with the prevalence of HIV infection both among the general population and among patients with tuberculosis [92,93,94,95,97]. According to the World Health Organization (WHO), among the 10.4 million TB cases in the world in 2015, 1.2 million are people living with HIV. To the 1.4 million deaths from tuberculosis that occurred in the world in the same year, according to WHO estimates, 400 thousand deaths of HIV-infected people associated with tuberculosis are added.

There has been an increase in the number of countries collecting the necessary reporting on detection, treatment and deaths of TB / HIV patients, and on chemoprophylaxis of TB among people living with HIV. The overwhelming majority of TB / HIV infections and deaths occur in countries in the WHO African Region [14].

In the Russian Federation, the prevalence and incidence of tuberculosis among the population tends to decrease, while the same all-Russian indicator for HIV-infected persons, on the contrary, is growing every year [12,39,50]. The incidence of severe forms of the disease in HIV-positive patients infected with *Mycobacterium tuberculosis* also increases [5,103].

According to WHO estimates, in 2015 in the world 1.1 million (1.0-1.3), or 11% (9.1-14%) 3 new cases and relapse of tuberculosis are associated with HIV infection. The highest value of the indicator was obtained for the countries of the WHO African Region - 31% (25-37%). For the countries of the WHO European Region, the value of the indicator was - 8.4% (7.0-9.9%). Among the countries of this WHO region is the Russian Federation, for which the values of the considered indicators were equal - 9.9% (8.8-11.0%), or 11.0 (9.3-13.0) thousand patients with combined pathology. Based on WHO estimates in 2015, a list of 30 countries with the highest burden of TB / HIV was identified, which are priority countries in terms of combating HIV-associated tuberculosis [97]. Twenty of them were included in the number of TB / HIV NSS countries due to the significant

number of cases of co-infection, determined as a result of the WHO assessment, and 10 countries - due to the high values of the estimate of the incidence of co-infection per 100 thousand populations. The highest proportion of tuberculosis patients tested for HIV (with known HIV status") was noted in the African, American and European regions of WHO - 81, 82, 72%, respectively [14].

Moreover, according to the researchers, a pre-trial detention center should be considered as a place where HIV infection and tuberculosis are often detected among persons in custody for the first time [22,51,74]. Thus, there has been an annual increase (by 10-20%) in the number of persons with tuberculosis among those released from prison compared with the number of newly admitted to places of imprisonment, which undoubtedly has a significant impact on the epidemiological situation among the civilian population [5,39].

In patients with generalized forms of tuberculosis, as a rule, the respiratory organs are also affected - in 91.4% of cases [68]. In this case, the lymph nodes inside the chest are very often involved. So there is evidence that in HIV-infected patients, tuberculosis of the intrathoracic lymph nodes occurs in 31.6% of patients versus 7.7% of those without HIV infection [4,76]

It should be noted that the number of cases of co-infection registered in the countries of the world reflects, as a rule, information generated only through national programs to combat tuberculosis [61]. This has a significant impact on the quality of supervision, reducing its completeness and information content. At one time in Russia, a system was created that allows to combine the movement of information about cases of combined infection from phthisiatricians, infectious disease specialists, pathomorphologists, doctors from medical institutions of the Federal Penitentiary Service of Russia into a single data bank [73]. At the same time, some efforts still need to be made to ensure that TB / HIV statistics and reporting are effective in the country.

Globally, according to 2015 data, among 501 thousand registered new cases and relapses of tuberculosis combined with HIV infection, about 391 thousand (78%) received ART. The value of this indicator has increased significantly compared to previous years, for example, it was equal to 36% in 2005 and 46% in 2010. In 30 NSS TB / HIV countries and 80% of TB patients who knew about a positive result of his HIV test, received ART. According to 2014 data [73], in the Russian Federation, ART covered 70.1% of TB / HIV patients and the resident population registered.

Pathogenesis and pathomorphology of tuberculosis. Late diagnosis of tuberculosis is due to both subjective and objective factors, in particular: insufficient phthisiatric alertness of general practitioners, the peculiarity of the pathomorphosis of tuberculosis, the presence of background diseases, and difficulties in the interpretation of morphological studies [55,59,62].

The onset of bacteremia is largely promoted by hypersensitization of the body due to a bacterial or viral infection, allergic disorders, vitamin deficiency, impaired protein and other types of metabolism, specific superinfection with prolonged and massive contact with bacteriophages, as

well as an immunodeficiency state and impaired phagocytic function of macrophages. Most often, generalization of the process occurs in hematogenous forms of tuberculosis - disseminated and miliary tuberculosis, which are the result of immune deficiency [38].

One of the features of the pathogenesis of HIV infection is the death of CD4 + T-helper cells, the concentration of which is slowly but steadily declining. In HIV-infected people, the CD4 + white blood cells decrease as the virus progresses. A low CD4 + cell count means the patient is immunocompromised. Acquired immunodeficiency syndrome (AIDS) is the terminal stage of HIV infection and develops in most patients with a decrease in the number of CD4 + T-lymphocytes in the blood below 200 cells / ml. AIDS is a complex of secondary diseases (B20-B24) that develop in HIV-infected people in the process of a significant decrease in immunity, manifested by specific diseases, including tuberculosis [48].

In HIV-infected patients, tuberculous meningitis occurs in the last stages of immunosuppression, when the CD4 + level is below 100 cells / μ l. Mortality in this group reaches 36.8-98% [4,68].

Features of the clinical course. In clinical and laboratory parameters, more pronounced anemia, leukopenia, lymphopenia, thrombocytopenia were noted. Indicators reflecting high functional load and liver damage are characteristic. Splenomegaly is typical of the objective examination data for patients with TB / HIV. The revealed features of the flow are confirmed by literary sources [9,65,75,77,78,103]. The high incidence of cardiac arrhythmias can be due to different etiologies: congenital malformations of the cardiovascular system, anesthesia, side effects of complex chemotherapy, exposure to penitentiary stress [30]. In addition, HIV can be an independent risk factor for cardiovascular disease. In persons suffering from TB / HIV, there are significant differences in the clinical picture and course of the disease, laboratory and instrumental parameters reflecting a more rapid and malignant course of the disease [21].

The portrait of a patient with generalized tuberculosis in combination with HIV infection is presented mainly by a young man with signs of social maladjustment. The duration of HIV infection before tuberculosis was detected in these patients averaged 7.2 ± 1.4 years. Among concomitant diseases, chronic viral hepatitis C, drug and alcohol addiction prevailed. In 2/3 of patients, tuberculosis was detected for the first time when contacting the general medical network. Common processes (disseminated pulmonary tuberculosis) prevailed, almost half of the patients had tuberculosis of the genitourinary system, a third of the patients had tuberculosis meningitis, tuberculosis spondylitis, and intestinal tuberculosis. One third of the patients were in serious condition, the same number of patients showed a change in consciousness. Half of the patients were diagnosed with leukopenia, and a third with lymphopenia. Bacterial excretion was detected in less than half of the patients, including 40% of MBT were not isolated from sputum, while a quarter of

the patients had drug resistance, of which 33.3% and 10% had multiple and extensive drug resistance, respectively. Disintegration of lung tissue and intrathoracic lymphadenopathy had almost half of the patients. In the majority of patients, tuberculosis appeared against the background of HIV infection in an extended stage with a decrease in the absolute level of CD4-lymphocytes, in 66.7% of patients - below 0.2×10^9 L [37].

Often, the clinical picture of patients with TB / HIV coinfection has an erased chronic course without specific signs [41]. However, there is information in the literature on the dependence of clinical and radiological manifestations of HIV-associated TB on the timeliness of detection [10]. In addition, depending on the severity of immunodeficiency, the tuberculosis process acquires a tendency towards an aggressive and acutely progressive course. According to the literature, disseminated and infiltrative TB prevail in HIV-positive persons in the structure of pulmonary forms, each occupying a share of about 30%. Extrapulmonary forms of TB are up to 2 times more common in HIV-positive individuals, and pulmonary forms are complicated by the combination with TB of extrapulmonary localization, leading to generalization of the process. In the late stages of HIV infection, TB is characterized by a predominance of generalized forms, a pronounced intoxication syndrome. Moreover, it can be accompanied by a decrease in the frequency of tissue destruction and bacterial excretion [43].

DIAGNOSTICS

The difficulty of establishing a diagnosis in many patients was due to a polymorphic, partly atypical clinical picture of the course of tuberculosis infection, which developed against the background of prolonged, uncontrolled intake of nonspecific anti-inflammatory drugs [55,59,62].

Systematic screening for tuberculosis in people living with HIV is an essential component of the WHO recommendations for the control of HIV and tuberculosis. According to 2014 data, from 76 countries, about 63% of HIV-infected patients who were observed for this disease ("enrolled in HIV care") were examined for tuberculosis. In the Russian Federation, the proportion of HIV patients with tuberculosis examinations reached 81.7% in 2014 [73].

The main methods of diagnostics and monitoring of pulmonary tuberculosis, which are currently used, are general clinical, radiation, laboratory, microbiological, molecular genetic, histological. Each of these methods has its drawbacks and cannot be considered absolute [42,69]. The clinical symptomatology of infectious pulmonary diseases is determined by the presence of intoxication and pulmonary syndromes, which do not have specific characteristics and therefore cannot be used as a reliable diagnosis of pulmonary tuberculosis [29,69,70,79].

Most patients turn to doctors of the general medical network when signs of any disease appear, both general and symptoms from individual organs and systems, including tuberculosis. For

the timely diagnosis of tuberculosis, an effective search is required in the form of constructive interaction between general medical doctors, therapists, surgical specialists, and morphologists [55,59,62].

Since the discovery of X-rays by V. X-rays, the X-ray method has been one of the main methods in the diagnosis of respiratory tuberculosis. The improvement of X-ray technology in recent years has made it possible to more accurately diagnose pulmonary tuberculosis, as well as to effectively control its treatment. Nevertheless, according to some authors, in connection with the clinical pathomorphosis of pulmonary tuberculosis, a frequent cause of diagnostic errors and difficulties in treatment is the erasure of differences in the clinical and radiological manifestations of respiratory diseases [31,58,69,84]. Accordingly, the role of such modern high-resolution X-ray diagnostic methods, such as digital tomosynthesis and multislice computed tomography, is increasing, which significantly increase the information content of the revealed changes in the lungs [52,53,98,107].

For more than a hundred recent years, detailed symptoms of tuberculous lesions of the lungs have been developed and are constantly being improved, depending on the form and course of the disease, algorithms for differential diagnosis have been developed [36]. Modern X-ray methods make it possible to identify and detail structural changes in the affected organ, to establish the localization, length, complications of the tuberculosis process [25]. The use of computer programs for transforming an image obtained in the course of ray studies is promising [57, 64]. However, the determined X-ray signs cannot be pathological only for pulmonary tuberculosis. On the basis of X-ray data, it is impossible to make a final conclusion about the genesis of morphological changes [35]. As a result, X-ray techniques need to be confirmed by other methods.

Determination of the presence of MBT in the patient's body is based mainly on the detection of specific antibodies. Historically, the first method is tuberculin diagnostics, which consists in detecting antibodies fixed on cells (lymphocytes, monocytes) when they interact with tuberculin. Currently, the intradermal test (Mantoux test) is widely used. This test retained its diagnostic value only among pediatric and adolescent patients, when its result is one of the diagnostic criteria [60]. In addition, tests with subcutaneous administration of tuberculin are of some auxiliary value in the diagnosis of tuberculosis, when they are guided by a characteristic general, local and focal reaction (Koch's test). "Diaskintest" is a new method for diagnosing tuberculosis disease and the state of infection, which is based on the determination of the reaction of the examined person's body to specific proteins that are found only in virulent strains of mycobacterium tuberculosis [40]. A positive Montour test result means that the person being examined has either been in contact with a tuberculosis infection, or has recently received BCG vaccination, or is infected with non-pathogenic mycobacteria that cannot cause disease and do not require any treatment [11]. Unlike the Mantua

test, a positive Diaskintest result indicates with a high degree of accuracy that the person being examined is either infected with tuberculosis at the moment or is already sick with it [69].

Recently, a new method for diagnosing latent tuberculosis, QuantiFERON TB-2G, has appeared, which is devoid of the drawbacks of a skin test [13]. It is based on the in vitro detection of interferon gamma production by the patient's blood lymphocytes. Antigens ESAT-6 and CFP-10 *M. tuberculosis* are used as inducers of interferon synthesis during its implementation. These antigens are expressed by *M. tuberculosis*, *M. bovis*, *M. africanum*, but they are absent in the BCG vaccine strain and most non-tuberculous mycobacteria, including *M. avium*, *M. intracellulare*. Thus, a high specificity of the test readings is achieved [27]. Increasing the sensitivity of the test and the objectivity of its readings is achieved by automating the detection of interferon. Tests carried out by Japanese specialists from the Tuberculosis Research Institute have shown that the specificity and sensitivity of the QuantiFERON TB-2G test are 98.1 and 89.0%, respectively [100]. Immunological diagnosis of tuberculosis is very promising [80]. However, to date, not a single serological test has been developed that has such a high sensitivity that it could replace the currently used methods of diagnosing tuberculosis [1, 69].

The central place in the systemic inflammatory response is the production of a wide range of proteins by the liver - acute phase reactants (POF), the changes in the concentration of which increase to varying degrees. The level of a number of proteins increases significantly (C-reactive protein (CRP), moderately (haptoglobin (HP), α 1-acid glycoprotein (AGP), α 1-protease inhibitor (α 1-PI), fibrinogen)), may remain within the reference range (ceruloplasmin (CP), α 2-macroglobulin (α 2-MG)) and require individual assessment, or may decrease (albumin, transferrin) [89]. The complexity of the analysis lies in the fact that they are polyfunctional and they are all capable of affecting one or several links of the inflammatory process [104]. Antioxidant properties are possessed by HP, AGP and CP. Direct antibacterial effects have been shown for CP and hemopexin, which bind copper and gem, respectively [87]. in inhibiting the activity of elastase-like and chymotrypsin-like proteinases coming from granulocytes to inflammatory exudates and causing secondary tissue damage. in different situations, it can act as both a pro-inflammatory and an anti-inflammatory agent [100]. An important modulatory component of the systemic inflammatory response syndrome is adenosine, the extracellular accumulation of which leads to a decrease in the activity of immune cells and to the protection of tissues from damage. One of the possible ways to study the specified relationship between adenosine and the functional state of immune cells is to study the activity of adenosine deaminase, which regulates the level of adenosine, converting it into inosine [6,89].

Bacteriological verification methods. The development and implementation of promising technologies for the accelerated diagnosis of TB and the determination of the causative agent's LP

are extremely important to ensure highly effective treatment based on the selection of personalized chemotherapy regimens. One of the most promising and demanded directions in the development of laboratory TB diagnostics, which is supported by WHO, the Global Laboratory Initiative and the European Laboratory Initiative, is the use of molecular genetic methods (MGM) [108].

More than a century of experience of phthisiatricians around the world has proved that the "gold" standard for diagnosing tuberculosis is the classic combination of microscopic and cultural methods of MBT research, which remain relevant today, despite the emergence of a large number of alternative methods. Bacterioscopic examination is the most accessible, fastest and cheapest method for detecting acid-fast mycobacteria [56]. However, the limits of the method, even with the use of the most advanced microscopic technology, including luminescence, make it possible to detect acid-resistant mycobacteria when their content is not less than 10,000 microbial bodies in 1 ml of material. This amount of mycobacteria is found in sputum only in patients with common, progressive forms of tuberculosis [3]. With a slight severity of the tuberculous process in the lungs, only 34% of patients manage to detect the pathogen during bacterioscopy of a smear from sputum, even after repeated examinations. In the absence of visible changes on radiographs, the detection of mycobacteria in a sputum smear is unlikely. A Nano immunofluorescence method has been developed for the rapid detection of tuberculosis bacteria in pathological material [46]. It is carried out using silicone nanoparticles with covalently immobilized protein A. In sensitivity, it is significantly superior to the fluorescent method for diagnosing tuberculosis. The use of an epifluorescent filter makes it easier to record the test results and reduces the time required for this [106].

The culture method for detecting mycobacteria is more sensitive and has a number of advantages over the microscopy method [24]. It allows you to identify MBT in the presence of several dozen viable individuals of the pathogen in the pathological material under study. A very important advantage of the method is the possibility of obtaining a culture of the pathogen, which can be studied in detail, identified and studied in relation to drug sensitivity, virulence and other biological properties. There are real opportunities to improve the efficiency of classical methods of microbiological research by improving the methods of material preparation, the use of new dyes, modification of cultivation systems and registration of the growth of mycobacteria, for example, the use of automated systems such as VASTEC MGIT 960 [45]. Reproduction of tuberculous mycobacteria in liquid nutrient media occurs much faster than in solid media [69].

The use of the PCR method for the diagnosis of tuberculosis makes it possible, within 1 working day (2-3 hours), to establish the presence of MBT DNA in the diagnostic material. Preference is given to test systems with real-time result detection, which almost completely eliminate the risk of sample contamination with amplification products [81].

The most promising method for determining genotypic LN is real-time multiplex PCR. The advantage of this method over the technologies described above is the absence of a hybridization stage and an assessment of the results in real time, which reduces the possibility of contamination. An example of such test systems is GeneXpert MTB / RIF (Ceiphid, USA). However, this test system determines resistance only to rifampicin (specificity 90% [13]) and is characterized by a very high cost of analysis. Of the Russian PCR test systems for the determination of MDR, one can note "Amplitub-MDR-RV" manufactured by CJSC "Syntol" (specificity for rifampicin and isoniazid is about 94%) [18,44].

Direct methods for detecting MBT include methods for detecting specific fragments of the pathogen DNA chain in the test samples of diagnostic material. Among the molecular biological techniques used for this, the most widespread method is the polymerase chain reaction (PCR), which is based on a multiple increase in the number of copies of a specific DNA region (the so-called directed DNA amplification) [2]. The method is especially relevant for tuberculosis, since it is effective against pathogens with high antigenic variability (including L-forms), the determination of which requires long-term cultivation or complex nutrient media, as well as against intracellular parasites and persistent microorganisms [32]. Along with this, PCR diagnostic methods are very promising for interspecies and strain identification of mycobacteria for the differentiation of tuberculous and non-tuberculous mycobacteria (causative agents of mycobacteriosis), for the rapid determination of drug resistance of mycobacteria [17].

The method of histological examination of tissue affected by a specific process is referred to as reliable methods for diagnosing tuberculosis. It allows the detection of granulation tissue and caseous necrosis, specific for tuberculosis, in biopsy material. This invasive method should be used in the most difficult cases of pulmonary tuberculosis diagnosis. However, the information content of histological examination is limited by the relative specificity of the tuberculous granuloma [33]. Similar morphological changes occur in sarcoidosis and other granulomatous processes. In addition, in patients with immunodeficiency (AIDS, hemoblastosis, immunosuppressive therapy, cytostatic therapy), the formation of tubercles is impaired or they are not formed. Histological examination of biopsy material, bacteriological examination on solid and liquid nutrient media, including using the Bactec MGIT - 960 system and molecular genetic diagnostics (Geno Type MTBDR plus (Hein test) and Xpert MTB / R1F) are referred to as methods of diagnosis verification. ... Clinical anamnestic, Xpert MTB / R1F, X-ray, bacterioscopic, skin tests with tuberculin, Diaskintest, GUANTIFERON - TV GOLD methods are referred to as screening research methods [26]. Currently, bacterioscopic and bacteriological (and their modifications) research methods are still the "gold standard" in the diagnosis of pulmonary tuberculosis.

Modern methods of diagnosing pulmonary tuberculosis (PCR diagnostics, serological diagnostics) are being actively introduced into practical health care and are increasingly important in the diagnosis of tuberculosis, however, they must be confirmed by bacterioscopic and / or bacteriological research methods.

The morphological method for confirming tuberculous pathology is reliable, but in many cases it should be borne in mind that there are limitations to its use.

Currently, despite the availability of a variety of modern methods for diagnosing tuberculosis, there is a need to develop and introduce new methods for rapid, high sensitivity and specificity of diagnostics [69].

THE CURRENT STATE OF TREATMENT AND PREVENTION

In the absence of treatment or irregular use of antiretroviral and anti-tuberculosis drugs in HIV-positive patients, as a rule, the most severe generalized (55%) and disseminated (15%) forms of tuberculosis develop, which is associated with a sharp weakening of immunity in this group of patients due to a violation coordinated work of Th1, Th2 lymphocytes and macrophages responsible for the elimination of mycobacteria and delimitation of caseous necrosis in the focus, as well as with the formation of multidrug resistance (MDR) of tuberculosis pathogens [5,12,39,103].

What matters is the quality of the chemoprophylaxis of tuberculosis. The stage of the disease or its classification determines the strategy of CP for people with HIV infection. CP is prescribed to patients with reduced immunity when registering cells + CD4 less than 350 in 1 µl. The best results in reducing the risk of developing tuberculosis in HIV-infected patients are observed while taking anti-tuberculosis and antiretroviral drugs [48].

The interaction of services to combat tuberculosis and HIV infection is a necessary link in the organization of identification and adequate treatment of patients with co-infection and prevention of the spread of tuberculosis among patients with HIV infection [92,94,95]. Collaboration between tuberculosis and HIV control programs should follow the following lines [61]:

- development of infection control measures,
- examination of tuberculosis patients for HIV infection,
- providing antiretroviral therapy (ART) to TB / HIV patients,
- organization of intensive examinations and active detection of tuberculosis among people living with HIV,
- Isoniazid prophylaxis of tuberculosis in persons living with HIV infection.

Standard controlled chemotherapy for tuberculosis is highly effective in treating tuberculosis caused by a sensitive pathogen [19, 28].

Conducting a microbiological study of the MBT drug sensitivity to the main and reserve anti-tuberculosis drugs is necessary in each case of isolation of the MBT culture. After receiving data from a microbiological study of MBT drug sensitivity, it is necessary to correct chemotherapy and prescribe individualized treatment regimens [65]

Treatment of MDR-TB patients is long-term with multicomponent chemotherapy regimens, often accompanied by adverse reactions (ADRs) to the drugs used and their combinations. This, especially in the absence of proper motivation and psychological support, increases the risk of withdrawal from treatment among patients, thereby increasing the likelihood of an unfavorable outcome [90,101]. Even an improvement in the patient's condition and a decrease / disappearance of the symptoms of the disease can be the reason for the patient's premature termination of the chemotherapy course due to an incorrect assessment of his condition [71].

An order for the Sverdlovsk region (2004) provided for the immunization of children born to mothers with HIV infection or a dubious HIV immunoblot against tuberculosis with the BCG-M vaccine in the maternity hospital after a commission decision on vaccination was made. Three years after the start of the order, an epidemiological analysis was carried out using a continuous method of results [49]. Data were obtained on the decrease in MBT infection and tuberculosis incidence in children born to mothers with HIV infection. The positive experience gained in the Sverdlovsk region made it possible to remove HIV infection in the mother from the contraindications to BCG-M vaccinations for a newborn in a maternity hospital [54].

At the end of 2015, 14,587 children were born to mothers with HIV infection in Russia. From mothers with HIV infection in 2013-2015 0.8% of children were born out of all those born alive in maternity hospitals in Russia. HIV infection was subsequently confirmed in children born to mothers with HIV infection: 2009 - in 6.7%, 2014 - in 6.2%, 2015 - in 6.1% of cases. Nevertheless, some children born to mothers with HIV infection are still not vaccinated with the BCG vaccine in the maternity hospital. The national calendar of preventive vaccinations is not fully implemented, the proportion of children vaccinated with BCG vaccine in maternity hospitals in Russia is decreasing: 2005 - 89.1%, 2014 - 85.5%, 2015 - 84.6% [48].

Anti-tuberculosis alertness is also relevant due to the prevalence of complex and atypical forms of tuberculosis in HIV-infected individuals, the high frequency of tuberculosis relapses after treatment, as well as the ineffectiveness of standard anti-tuberculosis therapy against the background of HIV infection [5].

According to the 2013-2014 cohorts. the effectiveness of treatment for newly diagnosed patients without and with HIV infection is 84.2 and 56%, respectively, and the mortality rate is 4.8 and 23.4%, respectively. The effectiveness of treatment of relapses of tuberculosis without and with

HIV infection is 68.4 and 47.4%, respectively, and the mortality rate is 10.8 and 22.8%, respectively [66].

In the conditions of an unfavorable epidemiological situation for tuberculosis, which, along with the aggravation of the structure of the clinical forms of a specific process, is a manifestation of the modern pathomorphosis of this disease, acutely progressive forms of pulmonary tuberculosis have acquired particular importance, a clear knowledge of the diagnostic and treatment tactics of which is necessary for every doctor [34].

The need for surgical treatment of tuberculosis in patients with HIV infection arises when anti-tuberculosis chemotherapy is insufficiently effective or when the course of the disease is complicated. This is most often the case with drug-resistant tuberculosis. The results of operations for pulmonary tuberculosis in patients with HIV infection (2.0% of postoperative complications associated with surgery, 1.2% of complications not directly related to surgery, 0.9% of deaths) are comparable to those in patients with tuberculosis with HIV-negative status [88,99,105].

The data obtained did not make it possible to clarify the information on the safest level of CD4 + lymphocytes for elective operations for respiratory tuberculosis. At the same time, resection operations were successfully performed in our patients with low CD4 + - who did not receive ART. This study confirmed that patients with CD4 + lymphocyte counts below 200 cells / μL have a high risk of complications and mortality, it was among 132 such patients that, after performing minor low-traumatic operations against the background of HIV infection progression, 3 (2.3%) lethal cases [67].

FORECAST

The mortality of patients with TB / HIV coinfection caused by the manifestation of tuberculosis infection is increasingly influencing the overall mortality of patients with tuberculosis [15.73]. This is due to an increase in the number of HIV-infected patients, among whom the manifestation of tuberculosis infection is the leading cause of death.

Thus, according to the estimated data published in the global report, tuberculosis, which is one of the ten leading causes of death of the world's population, taking into account the number of deaths of HIV-infected patients from the manifestation of tuberculosis infection, is already the fifth in importance. Deaths associated with the code B20.0 (or B20.7) increase the number of deaths associated with tuberculosis by almost a third [14].

As a result of the study, it was found that in the territory of high risk of tuberculosis and HIV infection, even with regression of the epidemic process of tuberculosis, accompanied by a decrease in the incidence of the entire population, HIV infection has a significant effect on its

tension, which, possibly, in the future may lead to a change the trend of the overall incidence of tuberculosis [82].

In the late stages of HIV infection with severe immunodeficiency, a significantly lower efficacy of TB treatment has been described, which is expressed in low rates of clinical cure, closure of decay cavities and cessation of bacterial excretion [9,41,65,75]. A particularly difficult treatment process is the combination of HIV infection and drug-resistant forms. Despite the lower incidence of multidrug / extensively drug-resistant TB among HIV-positive people, obtained in the study, a high incidence of adverse outcomes has been described in cases of treatment of resistant forms of HIV-associated TB [77].

At the same time, the average duration of illness until death is higher among patients of penitentiary institutions (3.2 ± 0.48 years) than in the analyzed data from literary sources [9,77]. This is facilitated by the presence of strict control over the intake of drugs by medical personnel in correctional institutions. It should be noted that for the branches of the "Tuberculosis Hospital" of the medical and sanitary units of the Federal Penitentiary Service, the problem of TB / HIV co-infection is most urgent. In specialized anti-tuberculosis medical and correctional institutions, the proportion of cases of somatic pathology, such as cardiovascular, trauma, auto aggression, and diseases of the gastrointestinal tract, decreases in the structure of mortality up to cessation. The cause of mortality is an infectious pathology, the share of cases in which TB / HIV co-infection is the overwhelming majority. At the same time, the proportion of acutely progressive and advanced chronic forms of tuberculosis decreases in an isolated course without HIV infection [62].

CONCLUSION

Thus, in the world literature, there are quite enough scientific works devoted to the problem of HIV-associated tuberculosis, but the problem is urgent and requires further research, with the search for new methods of immunotherapy and optimization of modern methods of diagnosis and treatment. The factors influencing the effectiveness of complex treatment, methods of rehabilitation and improving the psychoemotional state of patients in this category have not been studied enough.

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