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THE USE OF PLASMAPHERESIS AND INTRAVENOUS LASER BLOOD IRRADIATION IN TREATMENT OF PATIENTS WITH NEWLY DIAGNOSED TUBERCULOSIS AT THE LATE STAGES OF HIV INFECTION (references review)

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This article presents an overview of the current domestic and foreign literature on the problems of treatment of newly diagnosed tuberculosis in patients with late stages of HIV infection. The urgency of the problem, peculiarities of the clinical course and treatment of tuberculosis, the principles of antiretroviral therapy in the combination of tuberculosis and HIV infection are considered. It has been established that long-term chronic (или "long term" или "chronic") tuberculosis intoxication, as well as aggressive antituberculosis therapy, lead to disruption of metabolic processes, hypercatabolism, intoxication, and development of hypercoagulable syndrome. At the same time, data is provided on the toxic effects of antiretroviral therapy. Treatment of adverse reactions begins with detoxification and antihistamine therapy followed by the addition of vitamin therapy, antioxidants, antihypoxants, hepatoprotectors, anabolic agents, and enterosorbents. Various methods of pathogenetic therapy are of great interest, including extracorporal hemocorrection (plasmapheresis) and intravenous laser irradiation of blood (ILIB). Plasmapheresis (PA) allows the effective and short time normalization of homeostasis indices as well as reduction or elimination of intoxication effects, toxic and allergic reactions, hence increasing the effectiveness of basic therapy. Course of PA in patients with common forms of tuberculosis (3-5 procedures, with an interval of 2-3 days, removal of 20-25% of the volume of circulating plasma and replacement with crystalloid solutions in combination with hydroxyethyl starches) allows the elimination of symptoms of intoxication, increases tolerance of the organism to chemotherapy, and suppresses undesirable side effects. The method of quantum therapy (ILIB) is based on the effect of quantum energy on blood directly in the vascular bed. As the result photo bio-

logical influence of ILIB, all body systems are activated to correct the existing disorders. This is manifested to a great extent in tissues suffering from oxygen deficiency, since it is in these areas the metabolism increases and the processes of tissue reparation are activated. ILID helps for activation of white blood cell function, phagocytosis, synthesis of antibodies, interferon, and in general, improves the immune status.

Keywords: *tuberculosis, HIV infection, plasmapheresis, intravenous laser irradiation of blood.*

During the period from 2011 to 2015 the number of patients with initially registered antibodies to HIV in the Russian Federation has been steadily increasing (from 67,317 to 100,220). Similarly, during this period the incidence of HIV infection has increased (47.1 to 68.5 per 100,000 of the population). In this same period, the number of HIV – infected patients with newly diagnosed tuberculosis has steadily increased (from 11,839 to 16,100). The incidence of TB amongst HIV-infected patients has also increased (1881.5 to 2043.1 per 100,000 population) [1].

Tuberculosis in patients with AIDS is one of the most frequent and earliest opportunistic infections, reaching 50-75% of the total number of all cases of lung infection [2]. WHO estimates that in the early 21st century about 9 million new tuberculosis cases developed annually and nearly 10% of them ware combined with HIV infection [3,4]. The overall situation on HIV infection in different countries of the world is deteriorating with a tendency of becoming a generalized epidemic [5], which confirms the relevance of the research problem.

The clinical course of tuberculosis in the later stages of HIV infection. The course of tuberculosis depends on the duration of HIV infection and is determined by the degree of loss of the immune response [6]. In the period of the subclinical stage of HIV infection (stage-3), when the $CD4^+$ cell count ≤500/μl, the incidence of TB does not exceed the general population and is often associated with close contact with a person with bacterial excretion [7]. During this period HIV infection has practically no effect on the course of tuberculosis. Among clinical forms the infiltrative and disseminated subacute process are most frequently registered. If in this period, chemotherapy is inadequate or occurrence of a low treatment adherence, transformation into fibrous-cavernous, chronic disseminated or cirrhotic forms takes place [8]. In the later stages of HIV infection (4B, 4C) with the progression of immunodeficiency, tuberculosis acquires primary features with a tendency towards loss of lymphoid tissue, serous membranes and lympho-hematogenous dissemination [9]. At lower levels of $CD4^+$≤ 200/μl, the clinical picture of tuberculosis loses its typical manifestations, and is characterized by malignant and acute-prognosis course. The subsequent predominant processes include; tuberculosis of intrathoracic lymph nodes with bronchopulmonary component, disseminated miliary processes, pleural damage and tuberculous sepsis. The clinical features are manifested by pronounced intoxication syndrome with debilitating febrile reactions from low grade to high figures [10].

The more HIV infection-induced immunodeficiency is pronounced, the more the development of multiple tuberculosis sites. Extra pulmonary manifestations of tuberculosis occur amongst 30-70% of patients with $CD4^+$≤ 200/μl [57]. The course of tuberculosis in this period is characterized by formidable TB complications: meningoencephalitis, tuberculosis of intestines, peritoneum and abscessed middle adenitis, thereby increasing the probability of death [11].

Treatment of tuberculosis in patients with HIV infection. Chemotherapy (CT) of tuberculosis in HIV infection should be initiated immediately after diagnosis [12]. Currently, no convincing proof exists that the prolongation of therapy over 6 months in patients with HIV infection improves treatment results [13]. However, majority of researchers believe that prolonged treatment (up to 8-9 months) in these patients is more preferable because there is a decrease in the number of relapses [14]. Even when drug sensitivity is in-

tact, patients with such severe forms as tubercular meningitis, meningoencephalitis, bone – joint tuberculosis, require a basic course of chemotherapy of not less than 12 months. [15]. In addition, even in the continuation phase, intermittent CT regimen it is not recommended in patients with HIV infection. CT regimens are assigned based on individual results of determination of drug resistance of the pathogen: I – in drug sensitivity, II – in mono-resistance to isoniazid or MDR, III – in empirical anti-TB therapy, IV- in multiple drug resistance (MDR), V – in extensive drug resistance (XDR) [16].

Antiretroviral therapy in patients with combined infection. The combination of HIV and tuberculosis dictates a special approach to the prescription of antiretroviral therapy [17]. In patients with HIV – infection and tuberculosis with low $CD4^+$ count (≤100/μl) treatment starts with therapy of tuberculosis. If the patient tolerates TB therapy, antiretroviral therapy (ART) should be attached as early as possible (within 2-3 weeks (ART). Delayed ART initiation may lead to development of secondary diseases and even death [18].

With initial $CD4^+$ cell counts of 150-350/μl, treatment of tuberculosis is started and ART is attached in the first 2 months of starting TB treatment. When $CD4^+$ cell counts are higher than 350/μl, anti-TB therapy (ATT) is designated, at the same time control of $CD4^+$ cells is carried out. If on the background of TB treatment $CD4^+$ cells ≤ 350 /μl, ART should be prescribed. With progression of tuberculosis in HIV – infected patients (even at CD4 count >350/μl) it is advised to initiate ART. After the completion of tuberculosis therapy ART is recommended to continue for all HIV – infected patients (even at CD4 count >500/μl) to prevent relapse of tuberculosis [19].

International and national recommendations on the principles of prescribing ART in patients with tuberculosis combined with HIV infection have a coherent character and discussions identify only the advantages and disadvantages of the existing and newly emerging anti-TB and antiretroviral drugs as well as their adverse drug interactions. In addition to clinical effectiveness, special attention is paid to the toxic effects of ATT, which has an adverse impact on the clinical and immune status of HIV-infected patients [20].

Toxic effects of anti-tubercular therapy in patients with co-infection. Progressive chronic tuberculous intoxication, as well as relatively aggressive drug therapy lead to disruption of metabolic processes, hyper catabolism and intoxication, which are endogenous in nature. Development of hypercoagulability syndrome, which is the main cause of disturbance of microcirculation of blood in the organs, reduces the efficiency of basic therapy. Recovery of microcirculation in patients of tuberculosis with HIV infection is of great importance and is one of the determining factors for successful treatment [21,22].

Virtually all major anti-TB drugs can cause a variety of toxic and allergic reactions, causing failure of various organs and systems. According to different authors, the incidence of adverse effects of etiotropic therapy for tuberculosis ranges from 13-17% to 62-65% [23]. The development of neurological disorders, dysfunction of the gastrointestinal tract, allergic and hematological reactions, articular syndrome, urinary pathology, impaired function of the visual and auditory organs, etc. are the most often observed. Side effects of anti-TB drugs is one of the main reasons for the lack of effectiveness of chemotherapy [24].

Toxic effects of antiretroviral therapy in HIV-infected patients. In the recent past at least 25% of patients with HIV infection have discontinued ART during the first year of treatment because of the side effects. Tolerability of ART has improved significantly over the past three years thanks to the advent of new drugs in clinical practice, which led to a decrease in the incidence of discontinuation of ART due to side effects [25].

The most frequent toxic reactions with ART include: gastrointestinal disorders (loss of appetite, diarrhea, nausea, vomiting, heartburn, pain and bloating); from liver diseases to development of liver failure; from kidney dysfunction (renal lithiasis) to development of renal failure; neurological side effects (peripheral neuropathy, disorders of the central nervous system); allergic reactions: from skin rashes, lesions of mucous membranes to anaphylactic

shock; and the occurrence of avascular necrosis, osteopenia and osteomalacia [26,27].

A treatment of adverse reactions should be initiated with detoxification and antihistamine therapy, followed by the addition of vitamin therapy, antioxidants, antihypoxants, hepatoprotectors, drugs with anabolic action and enterosorbents. In modern conditions, practitioners are increasingly turning to various methods of pathogenetic therapy, the application of which aims at the correction of internal organs' and systems' metabolism, thereby improving reparative properties of the body. One of these methods is extracorporeal hemocorrection [28].

The use of plasmapheresis in patients with tuberculosis in the late stages of HIV infection. Methods of extracorporeal hemocorrection are directed to qualitative and quantitative change of cell, protein, water and electrolyte, enzyme, and gas composition of blood by treating the blood outside the body. Modern methods of hemocorrection allow effective and short time to normalization of homeostasis, reducing or completely eliminating the symptoms of intoxication, toxic and allergic reactions, thus increasing the efficiency of basic therapy. Plasmapheresis (PA) is the most effective generic method of detoxification of the body that removes various substrates present in plasma, regardless of their nature or molecular weight [29].

Currently, this method is increasingly used in TB clinics. Indications for plasmapheresis in patients with tuberculosis are: intoxication of any origin and of any degree of manifestation; the appearance of toxic and allergic reactions to anti-TB and other drugs in patients; aggravation or manifestation of accompanying diseases: hepatitis of various etiologies, hepatic failure (acute and chronic), diabetes and its complications, peritonitis, vascular lesions of the lower limbs, followed by trophic ulcers, purulent diseases of soft tissues, pancreatitis, correction of hypercoagulation syndrome [30].

The use of PA and hemosorption allows to effectively reduce toxicity in acutely progressive forms of tuberculosis. Studies have shown that the direction of PA in patients with disseminated forms of tuberculosis (3-5 procedures with an interval of 2-3 days, removing 20-25% of volume of circulating plasma and replacing it with crystalloid solutions in combination with hydroxyl-Ethyl-starch) allows quick elimination of symptoms of intoxication, increase the body's tolerance to chemotherapy and stops unwanted side effects. The use of PA increases the efficiency of treatment of TB, contributing to the cessation of bacterial excretion (in 89% of cases) and closure of decay cavities (63%) [31,32]. In addition to PA, there are other in vitro methods of exposure to blood – such as intravenous laser irradiation of blood (ILIB), ultraviolet irradiation of blood (UIB) and ozonation, which significantly increase the patients' chances of a favorable clinical course of tuberculosis [33].

The application of intravenous laser irradiation of blood in patients with tuberculosis in the late stages of HIV infection. Intravenous laser irradiation of blood (ILIB) is one of the methods of quantum therapy, which is based on the effects of quantum energy on the blood directly into the bloodstream. This is a unique method of photo biological influence, in which all body systems are activated towards correcting existing discrepancies. Effects of ILIB are more pronounced in tissues experiencing oxygen deficiency, as it is in these areas of increased metabolism that tissue reparation processes are activated. Activation of leukocytes contributes to the synthesis of antibodies and interferon, activation of phagocytosis, hence generally improving the immune status [34].

ILIB was first used in patients with tuberculosis when its influence on the improvement of rheological properties of blood (reducing the level of toxic products of metabolism as well as the propensity to thrombosis) were proven [35]. Application of customized laser therapy was tested in the initial stages of complex chemotherapy in patients with primarily diagnosed destructive pulmonary tuberculosis. It was noticed that the use of laser therapy significantly increases the effectiveness of treatment, contributing to the cessation of bacterial excretion and healing of decay cavities as well as reduction of the length of hospital stay for 1.5-2.5 months [36].

Similar results were obtained by researchers who noted that the application of

ILIB in complex treatment of tuberculosis patients increased achievement of clinical cure and full medical and social rehabilitation by 1.3-1.5 times [37]. The therapeutic effects of intravenous irradiation of blood in patients with tuberculosis in enhancing immunity are realized by; improving blood microcirculation, vasodilator and analgesic actions, improvement of oxygen-transport function of blood, normalization of metabolic processes (protein, lipid, carbohydrate, intracellular energy balance), as well as stimulation of regenerative processes [38].

Indications for ILIB treatment include a large group of infectious diseases, including HIV. Comprehensive HIV treatment (with the use of ILIB) has immunocorrective effect on cellular immunity, normalizing the contents of IFN – α/β and IFN-γ, yet having no effect on humoral immunity: IgA, IgM and IgG [41]. White blood cells – macrophages, T- and B-lymphocytes, granulocytes are also activated under the influence of ILIB, resulting in mobilization of cells and improving cell-to-cell communication. This leads to an increase in cellular and humoral immunity, bactericidal properties of blood, which is important for the treatment and prevention of secondary diseases in HIV-infected [39].

Conclusion

In the light of this, the world scientific community carried out a sufficient amount of scientific research on the clinical and immunological features of late stages of HIV infection and epidemiology, clinical peculiarities and diagnostics of combined (TB/HIV) infections. Success in the management of such patients belongs to the collegial management of infectious disease specialists and TB specialists, the timely appointment of PTT and ART under the control of the immune status, the appropriate treatment of toxic and allergic side reactions, including using in vitro methods of treatment. However, data on the use of plasmapheresis and intravenous laser irradiation of blood in patients with tuberculosis in the late stages of HIV infection is insufficient and not of conceptual nature, therefore research in this direction represents great scientific relevance and practical significance.

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