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TB and HIV in the Russian Federation: Risk Factors of MDR-TB in HIV-infected Patients (review)

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Туберкулез и ВИЧ-инфекция в Российской Федерации: факторы риска МЛУ-ТБ среди пациентов с ВИЧ-инфекцией (обзор)

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Summary

In the article, a review of foreign and Russian literature suggests that both multidrug-resistant tuberculosis spread and the HIV epidemic are factors maintaining the high tuberculosis burden worldwide and in the Russian Federation.

The main transmission pathway for HIV-infection in the Russian Federation, as well as in other countries of Eastern Europe and Central Asia, is now attributed to heterosexual contact, which has surpassed the intravenous injection route of transmission. A rise in heterosexual risk of HIV transmission is accelerating epidemic progression amongst the general population, thereby contributing to a generalization of the epidemic process.

The authors also provide an analytical review of publications related to risk factors for multidrug-resistant tuberculosis development in HIV-infected patients. It is found that such literature is limited in foreign countries, as well as in the Russian Federation. There is information about the general role of HIV infection in tuberculosis burden, but the influence of socio-demographic, epidemiological and clinical factors for multidrug-resistant tuberculosis development in people living with HIV is not sufficiently studied. Thus, there is a need for further studies designed to analyze the socio-demographic, epidemiological and clinical characteristics of patients with multidrug-resistant tuberculosis and HIV co-infection in comparison with those who are HIV-negative. Knowledge of the main risk factors for multidrug-resistant tuberculosis development in people living with HIV will allow selective and targeted use of resources to achieve effective outcomes in treatment of HIV/TB co-infected patients.

Keywords: HIV-infection, tuberculosis, HIV/TB co-infection, MDR-TB in HIV, Russian Federation, Eastern Europe and Central Asia

Резюме

В статье представлен обзор зарубежных и российских научных публикаций о распространении туберкулеза с множественной лекарственной устойчивостью воз-

будителя и ВИЧ-инфекции как основных факторов, влияющих на сохранение высокого бремени туберкулеза в мире, в Российской Федерации.
Основным путем заражения ВИЧ-инфекции в Российской Федерации, как и в других странах Восточной Европы и Центральной Азии, в настоящее время становится рост гетеросексуальных контактов, сменивший внутривенный инъекционный путь инфицирования вирусом иммунодефицита человека, что усиливает распространение заболевания среди общей популяции и способствует генерализации эпидемического процесса.
Авторами также проведен аналитический обзор публикаций, связанных с факторами риска развития туберкулеза с множественной лекарственной устойчивостью возбудителя у пациентов с ВИЧ-инфекцией. Установлено, что проведение таких исследований, как в мире, так и в Российской Федерации, ограничено. Имеются сведения о роли ВИЧ-инфекции в распространении туберкулеза в целом, влияние социально-демографических, эпидемиологических и клинических факторов в развитии туберкулеза с множественной лекарственной устойчивостью возбудителя у людей, живущих с ВИЧ, изучается недостаточно. В связи с этим возникает необходимость проведения исследований, направленных на анализ социально-демографических, эпидемиологических и клинических характеристик пациентов с сочетанием туберкулеза с множественной лекарственной устойчивостью возбудителя и ВИЧ-инфекции в сравнении с таковыми без ВИЧ-инфекции. Знание основных факторов риска развития туберкулеза с множественной лекарственной устойчивостью у лиц с ВИЧ-инфекцией позволит избирательно и целенаправленно использовать ресурсы для достижения эффективных результатов лечения пациентов с сочетанием туберкулеза и ВИЧ-инфекции.

Ключевые слова: ВИЧ-инфекция, туберкулез, сочетание ВИЧ/ТБ, Российская Федерация, Восточная Европа и Центральная Азия

Tuberculosis co-infection with HIV (HIV/TB) is one of the fundamental issues facing global health and continues to delay disease eradication. HIV affects tuberculosis (TB) progression by manifesting as accelerated transmission and advancement through stages of disease [1, 2] and in recent years, the development and spread of TB drug-resistance has complicated effective therapy and treatment outcome in patients with HIV-infection as well as without [3, 4]. In the Russian Federation, a worsening HIV epidemic necessitates improved measures to control the spread of HIV/multidrug-resistant TB (MDR-TB) co-infection, as well as in order to continue trends of TB decline [5, 6].

While a global estimate of 10 million people fell ill with TB in 2018, this number has remained relatively stable in recent years and has improved since 2010 [7]. In the Russian Federation, data from the WHO Global Tuberculosis reports indicate that incidence and disease mortality is decreasing more rapidly (5.4% per year) than in any other high-burden country worldwide [7].

Despite these trends of improvement, TB drug-resistance is on the rise, threatening public health and global TB eradication [8]. Patients who exhibit MDR-TB do not respond well to rifampicin and isoniazid, the two most effective first-line anti-TB drugs, and experience poorer treatment success following longer, more expensive treatment regimens [8, 9]. An even rarer manifestation is extensively drug-resistant TB (XDR-TB), which consists of MDR-TB that is additionally resistant to three or more of the six classes of second-line drugs [10]. TB drug resistance is known to arise through the selection of mutations in patients undergoing TB treatment regimens of low effectiveness or who poorly adhere to treatment, as well as through person-to-person transmission of drug-resistant *Mycobacterium tuberculosis (MTB)* [11]. Until 2011, the global problem of drug-resistant TB was not addressed directly as it was believed that advocacy of sputum-smear microscopy and first-line TB treatment alone would be most cost-efficient in resource-poor settings [5]. There are no effective preventative vaccines for drug-resistant TB, and the current BCG vaccine does little to mitigate the most common form of TB disease, pulmonary TB infection in adults [12].

Half a million new cases of rifampicin-resistant TB were estimated for 2018 worldwide, of which, 78% were considered MDR-TB [7]. By country, the largest shares of the MDR-TB global disease burden were attributed to India (27%), China (14%), and the Russian Federation (9%) and the highest proportions attributed to the former-Soviet countries (>50% of previously treated TB cases) [7]. In former-Soviet countries, a deterioration of TB control was attributed to the experienced social and economic destabilization following the disintegration of the Soviet Union, contributing as well to the rise in drug-resistant strains of *MTB* in the area [13]. While federal financial support for TB programs decreased in the 1990s, cessation of screening activities and insufficient drug supplies contributed to the emergence of TB drug-resistance, as well as to a nearly threefold increase in TB incidence and mortality over the course of eight years [13].

According to past monitoring data in the Russian Federation, the proportion of TB cases that achieve

smear-negation in patients with newly diagnosed TB does not exceed 70% [14]. For this reason the practice of surgical interventions, such as collapse therapy, for the treatment of TB are still widely used. The effectiveness of treatment of patients with destructive pulmonary TB is considered to be even lower and rarely to exceed 60% [14]. The argument for surgical intervention for smear-negation revolves around the belief that continued chemotherapy with second-line drugs contributes to an increase of a number of patients with MDR-TB and XDR-TB, whose share in the Russian Federation has already reached 40% [14]. In the Russian Federation, the mortality rate of MDR-TB is considered to be no less than 40% [15]. Amongst patients with MDR-TB worldwide, approximately 9–10% have XDR-TB, which bodes unfavorably for treatment outcomes [15].

Globally, in the same countries with the highest proportions of TB drug-resistance, rates of HIV infection have been on the rise [7, 16]. According to UNAIDS 2019 Data, Eastern Europe and Central Asia comprise one of two global regions where the annual number of AIDS-casualties have collectively increased since 2010 [16]. This region has been identified to have the fastest growing HIV epidemic in the world, where the annual number of HIV infections has reached 150,000, 29% higher than in 2010 [16]. Statistically, the Russian Federation and Ukraine comprised 84% of all new HIV infections in Eastern Europe and Central Asia, and exclusion of data from the Russian Federation results in a 4% decline in the region's 2010–2018 trend analysis regarding new HIV infections [16].

As higher proportions of HIV transmission in the Russian Federation were attributed to intravenous drug use in the past, recent evidence has shown that heterosexual transmission is increasing [17]. In 2016, 48% of those infected with HIV in the Russian Federation listed sex with heterosexual partners as the sole risk factor for infection [17]. In light of a shift towards heterosexual transmission, there runs a greater risk for HIV spread within the general population, which, if not efficiently addressed, will further propagate the current epidemic. As of 2016, the sociodemographic portrait of HIV patients living with HIV in Russia and visiting AIDS Centers did not differ from the distribution of citizens of the same age [18]. Across 27 regions of Russia, 7,000 patients were analyzed and determined to represent an economically and socially integrated population, whose average age fell at 34 years (18–79) [18]. As this study only concerned patients who were registered at regional AIDS Centers, it is important to note that there may exist HIV-infected populations that are currently not under observation or who are not receiving treatment. Drawing from epidemiological data from the Russian Northwestern Federal District in 2016, the highest rates of HIV detection were found amongst drug users, homosexuals and bisexuals, and the prison population [19].

At the present time in the Russian Federation, two reporting systems for HIV epidemiological monitoring are in place, operated in-country by Rospotrebnadzor and the Russian Ministry of Health [20]. In 2018, reports of newly diagnosed HIV cases between Rospotrebnadzor and the Russian Ministry of Health differed nationally by 33.4%, in the Northwestern District of Russia by 41.6%, and in Saint-Petersburg by 58.4%. These differences are attributed to the different strategies employed by the reporting systems, in which Rospotrebnadzor accounts for all newly positive immunoblots against HIV antibodies, while the Ministry of Health takes into account the number of new patients who register under dispensary observation with Regional AIDS Centers [20]. This evidence suggests that a large proportion of those who test positive for HIV are not receiving antiretroviral treatment (ART), and subsequently are not screened for TB.

Co-infection of HIV-1 and *MTB* increases the risk of active TB and rapidity of HIV-1 disease progression [21]. As the primary cellular targets of HIV-1 are $CD4^+$ cells, T cell lymphocytes that are a part of the body's immune system, immune defense is compromised against secondary and opportunistic infections [21]. After HIV-1 transmission, risk of developing active TB increases 2–5 fold, which increases to 20–fold after the onset of HIV-1 induced immunodeficiency [21]. The life-expectancy of HIV-positive patients is significantly compromised by TB co-infection, while epidemiology, clinical presentations, and management of HIV and TB infections are far more complex in the case of co-infection [6, 12]. While current WHO guidelines recommend that both MDR-TB and HIV require treatment immediately upon diagnosis, there are reasonable chances that clinically significant drug-drug interactions between MDR-TB agents and antiretrovirals impact treatment efficacy and safety, warranting further pharmacokinetic and pharmacodynamic investigation as well [22]. In order to effectively treat HIV-associated TB, anti-TB treatment must be integrated with ART, while simultaneously monitoring drug cytotoxicity, HIV-related comorbidities, and the development of immune reconstitution inflammatory syndrome (IRIS) [2].

In the Russian Federation, active TB infection is thought to affect 32–56% of HIV-positive patients in advanced stages of infection, a continuous leading cause of death within the HIV-positive patient population, as remains the case worldwide [23]. As is commonly observed in HIV-infected patients, TB granuloma formation may fail in immunocompromised individuals, manifesting as rapid generalization of TB disease [12]. Generalized TB in HIV-infected patients is known to be closely related to degree of immunodeficiency (r=–0,98), and in terms of extrathoracic localizations in HIV/TB, lesions of almost all organs are observed [24]. Bronchopulmonary symptoms are often not expressed in the co-infected patient popu-

lation, and chest X-ray may reflect presentations abnormal for TB in adults — damage to the intrathoracic lymph nodes, interstitial dissemination, and the absence of lung tissue destruction [24]. This complicates timely TB diagnosis in HIV-positive patient populations and, in the background of rapid disease progression, leads to inadequate treatment and high mortality [24].

Although global TB incidence has been trending on a decline, in developed countries, increased migration and HIV-infection attribute to a greater proportion of extrapulmonary TB [25]. Tuberculous spondylitis is a rare presentation of extrapulmonary TB that comprises 1–5% of all TB cases and 50% of bone and joint TB cases [25]. As the infection spreads through the vertebrae, the disease may lead to vertebral collapse and spinal damage, often resulting in neurological symptoms [25]. In HIV-infected patients, the severity of tuberculous spondylitis, assessed by disseminated forms and cases of multiple localization, are closely related to degree of immunosuppression [26].

From 2013 to 2017 in the Northwest District of the Russian Federation, a region considered to be well-controlled, the burden of patients with HIV/MDR-TB co-infection increased by 3.9 times (from 3.2% to 12.5%), a trend that will, if unaddressed, contribute to the slowing of the rate of TB decline [27]. Additional suggestions have proposed that the Russian Ministry of Health fully commit to financial and administrative needs at the level of local hospitals, targeting TB in vulnerable populations, such as children, those who suffer from TB co-infection, and people living with HIV [28].

In order to mitigate drug-resistant TB transmission within populations that exhibit a high burden of HIV-infection, there is recognition of an urgent need for the design of region-specific interventions [19, 29]. Their purpose would be to address implementation of rapid molecular diagnostics, assessment of regimen effectiveness, active screening of vulnerable populations and those who have come in contact with drug-resistant TB, as well as prophylactic measures [29]. In terms of HIV in the Russian Federation, it has been proposed that individual regions be classified based on current epidemic profile, based on whether HIV incidence in a defined area is increasing, decreasing, or has remained high in the past decade [19]. In this way, regional factors contributing to high HIV incidence can be assessed and analyzed in terms of drug trafficking, how informed the general population is about HIV-infection and drug use, ethnic and geographic characteristics, internal and external migration, effectiveness of prophylactic programs (i.e. anti-drug), economic resources in the region and financial support for HIV programs, and availability of laboratory and medical services [19]. Because of region-to-region variation across the Russian Federation, this strategy could simultaneously centralize epidemiological approaches, while tailoring interventions to consider the availability of regional resources.

The rise of MDR-TB resistance to fluoroquinolones and second-line injectable drugs as well as increased prevalence of XDR-TB challenges the effectiveness of current treatment regimens. In 2013, bedaquiline was approved for use in the United States and Europe for the treatment of MDR-TB/XDR-TB along with a WHO-approved background regimen and has since then been widely implemented in the Russian Federation [30]. Linezolid, which was approved by the FDA in 2000, has likewise been justified by tolerability and efficacy studies and has been used to treat drug-resistant TB in the Russian Federation since 2010 [31]. In 2013, delamanid also was shown to improve treatment outcome and reduce mortality in combination with an approved background regimen among MDR-TB and XDR-TB patients [32]. In recent years, delamanid has been licensed for use in the Russian Federation, but despite co-administration with bedaquiline in complex drug-resistant TB cases, combined use is not advised due to lack of evidence in regards to safety [33]. Perchlozon (4-thioureido-iminomethylpyridinium perchlorate), a Russian TB drug registered in-country in 2012, has been applied routinely in clinical practice and since then has been shown to increase the effectiveness of 6-month therapy for pulmonary MDR-TB, evaluated by smear negation and positive radiological dynamics [34]. As WHO recommendations propose that a minimum of 4 active drugs should comprise an effective drug regimen, it is important to monitor the development of adverse events arising throughout the long duration of MDR-TB and XDR-TB treatment [33]. Safety, tolerability, and effectiveness of combination drug regimens for drug-resistant TB should also be evaluated in respect to ART use.

Research surveying Eastern Europe has indicated that drug-resistant TB is associated with young age, low socioeconomic status and a history of incarceration [5]. HIV/TB co-infected patients in Eastern Europe constitute a similarly challenging population, characterized by high socioeconomic deprivation, intravenous drug use, hepatitis co-infection, and poor access to ART [11]. A 2017 study in Moscow identified that the following typical characteristics were more frequent in HIV/TB co-infected patients versus in HIV-negative TB patients: permanent resident of the city, between the ages of 31–40 years old, male, unemployed, no destruction of lung tissue, disseminated form of pulmonary TB, and previous incarceration [35].

Patients co-infected with HIV/TB may also be at increased risk than HIV-negative TB patients of developing MDR-TB, which has been attributed to a characteristic rapid disease progression in environments conducive to drug-resistant TB exposure [22, 36, 37]. Increased hospitalization of HIV-positive patients, nosocomial infection within TB facilities, contact with MDR-TB patients in the

midst of poor infection control, and a heightened risk of association with MDR-TB in prison settings have also been identified as possible contributors [36, 38]. In the Eastern European region, infrequent use of internationally recommended MDR-TB treatment regimens have also been reported, and rates of ART use and viral suppression fell below the targeted 90% [37]. A study concerning drug-susceptible and drug-resistant HIV-positive patient populations in Eastern Europe concluded that patients with MDR-TB were less likely to achieve cure or complete treatment (21.8% vs. 62.9%, $p<0.0001$) and were more likely to die (65.5% vs. 27.0%, $p<0.0001$) [11]. Another study conducted amongst patients throughout the Russian penitentiary system with XDR-TB showed that successful treatment outcome was poor at 21.4%, of which, 34.5% was attributed to treatment failure and 27.7% was attributed to patient discontinuation under observation [37]. Increased availability of high-quality laboratory diagnostics and continued use of collapse therapy in the penitentiary system have been proposed as possible interventions [37].

In a 2016 study in the Republic of Karelia, a high prevalence of MDR-TB was associated with late detection and delayed diagnosis of HIV/TB co-infection, where 70% of cases were classified as advanced stages of HIV [39]. Reaffirming a pressing need for efficient TB diagnosis, universal and systematic implementation of molecular diagnostic tools when TB is suspected in HIV patients, such as Gene-X-Pert, could improve treatment outcome through timely diagnosis of TB as well as determination of resistance to rifampicin [40]. Due to rapid TB disease progression and generalization in HIV-patients, a chest X-ray every six months may not be informative enough to achieve timely early detection [41]. Instead, employing several strategies, including assessing TB presentation in the intrathoracic lymphatic nodes, could strengthen criteria for timely diagnosis [41]. Inadequacies and difficulty in diagnosing TB amongst HIV-positive patient populations remains a problem in the Russian Federation, with greater than 80% of diagnoses made through passive case-finding [41].

In the Russian Federation, there exist additional challenges despite the fact that increased centralization of molecular genetic diagnostic methods has greatly improved the efficiency and accuracy of *MTB* detection [42, 43]. Timely TB detection continues to be difficult to achieve in the HIV-positive patient population due to rapid disease progression in the context of severe immunosuppression, however, factors such as marginalization stemming from psychosocial pressures and stigmatization may also play a role [44, 45]. A study at Botkin's Infectious Disease Hospital in St. Petersburg suggested moderate to high stigmatization amongst HIV-patients, with greatest emotional significance surrounding the disclosure of their diagnosis. It was shown that higher emotional burden associated with diagnosis disclosure correlated positively with a higher level of education [46]. In the Republic of Karelia, it was also noted that input of HIV/TB patients from the Federal Penitentiary System contributed significantly to disease distribution in the general population in this region [39]. In this way, increased social support for marginalized groups such as the homeless and the previously-incarcerated could improve monitoring among these risk groups, as well as ease disease burden within the general population [39].

Psychosocial factors may also play a role in the integrity of treatment adherence, preventing relapse and the development of drug-resistant TB, especially a challenge within key risk groups in the Russian Federation, namely migrant populations, intravenous drug-users, the homeless, and the prison population [11, 39, 37, 44, 47]. The incarceration of intravenous drug-users creates a situation of increased risk of HIV and TB transmission amongst prison populations, which is worsened by high levels of internal and international migration [48]. As acquired drug resistance was previously attributed to *de novo* mutations following poor treatment adherence, evidence following analysis has suggested that the bulk of MDR-TB cases may be attributed to transmission, where approximately 96% of new MDR-TB cases and 61% of previously treated cases were due to transmission [11, 49]. In this way, the exercise of greater control measures for screening and early diagnosis within high-risk populations could mitigate transmission of drug-resistant TB, thereby decreasing likelihood of co-infection with HIV.

At present day, evidence indicates that internationally recommended MDR-TB treatment regimens are infrequently adhered to in Eastern Europe, and difficulties in achieving adequate ART use and viral suppression were linked to non-cooperativity in the patient population and weaknesses in the sphere of health care [37]. In HIV-patient populations, urgent improvements need to be made in early and efficient TB diagnostics, increased access to- and implementation of second-line TB drugs, prompt ART initiation and viral load monitoring [6]. In this way, improved management of HIV/TB patients in Eastern Europe, especially those with MDR-TB, begins with systematization of HIV/TB diagnosis and treatment.

In review of Russian and international literature, there is little work that focuses on risk factors that may contribute to the development of MDR-TB within HIV-infected populations. As studies specific to the Eastern European region have shown that drug resistant TB and TB/HIV co-infection are significantly characterized by socioeconomic deprivation, it would be valuable to assess the degree of marginalization associated with the frequency of co-infection and the development of MDR-TB. Definitive evidence could help direct the implementation

of region-specific support measures for high-risk groups that are notoriously difficult to reach.

While significant progress has been made in the global reduction of TB infection, a rise in drug-resistant presentations of TB poses further complications for co-infection with HIV. In the Russian Federation, a reduction in HIV/TB and HIV/MDR-TB may require revisions for a centralized system of HIV reporting and region-specific strategies. Additionally, co-infected patients could benefit from an integration across specialties, namely in administering treatment for TB and HIV in one centralized location, so patients do not have to separately visit TB dispensaries and Regional AIDS Centers [50]. Greater control within high-risk populations to streamline early TB detection and treatment initiation, as well as treatment adherence, has the potential to reduce transmission of drug-resistant TB. Urgent action is needed to integrate TB and HIV interventions in the face of rising TB drug-resistance and a worsening HIV-epidemic in the Russian Federation [6, 47].

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