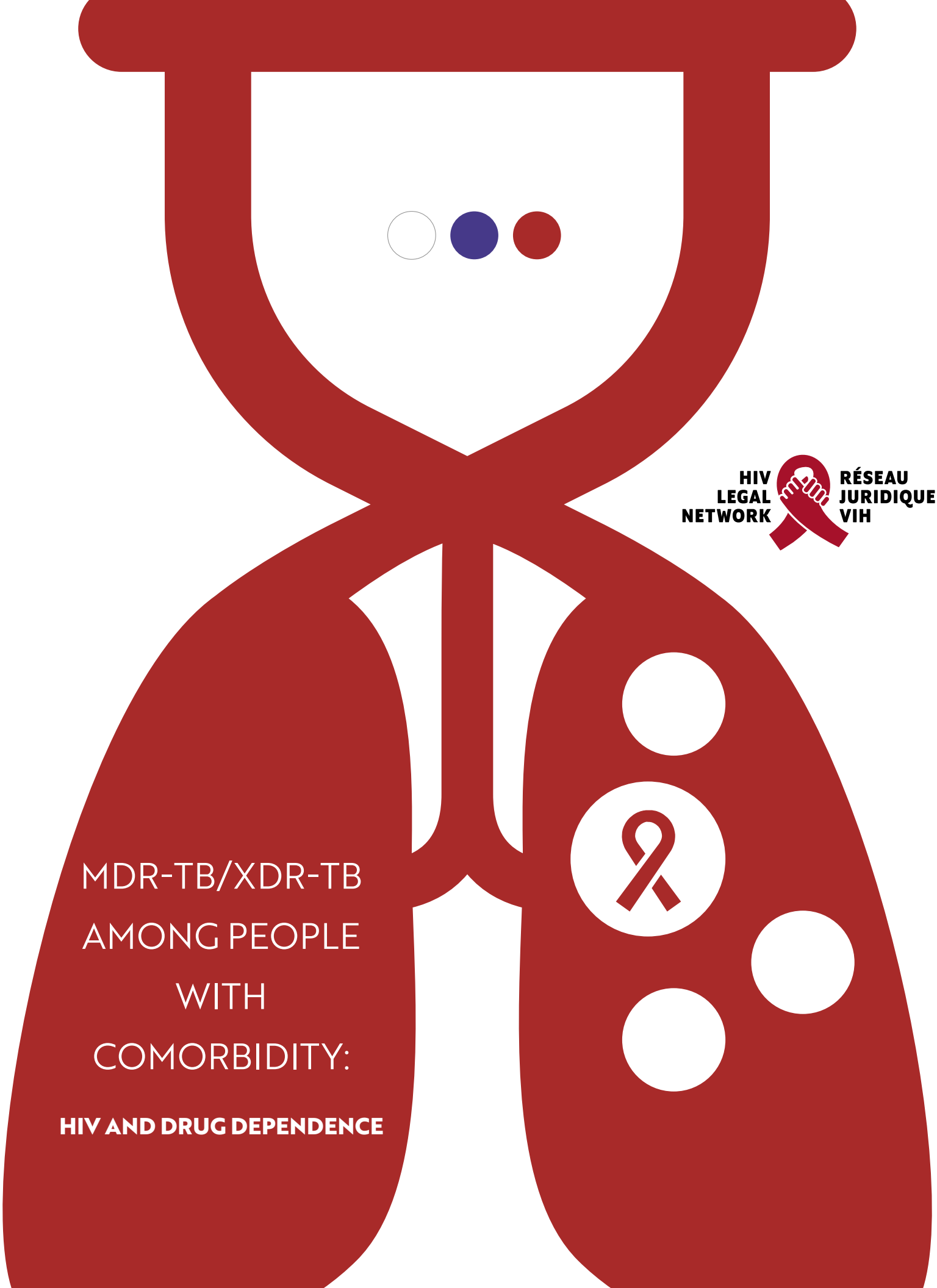


HIV LEGAL NETWORK

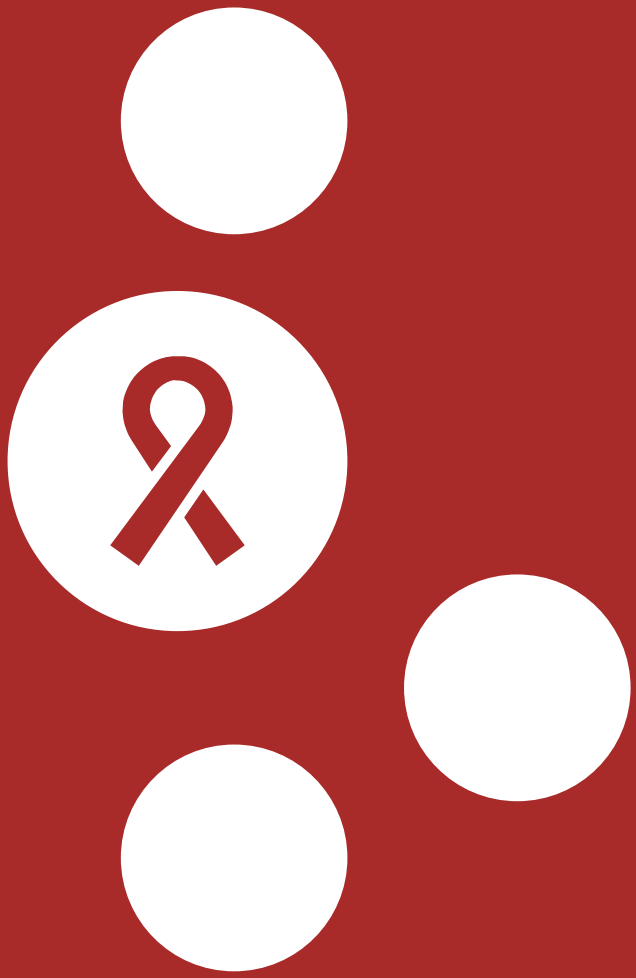
RÉSEAU JURIDIQUE VIH

MDR-TB/XDR-TB AMONG PEOPLE WITH COMORBIDITY:

HIV AND DRUG DEPENDENCE

Abbreviations

TB	Tuberculosis
MDR-TB	Multidrug-resistant TB
XDR-TB	Extensively drug-resistant TB
HIV	Human immunodeficiency virus
UN	United Nations
ATT	Anti-TB therapies



Acknowledgements

Authors: NY Sidorenko, MM Golichenko

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Graphic Design: Ryan White, R.G.D.

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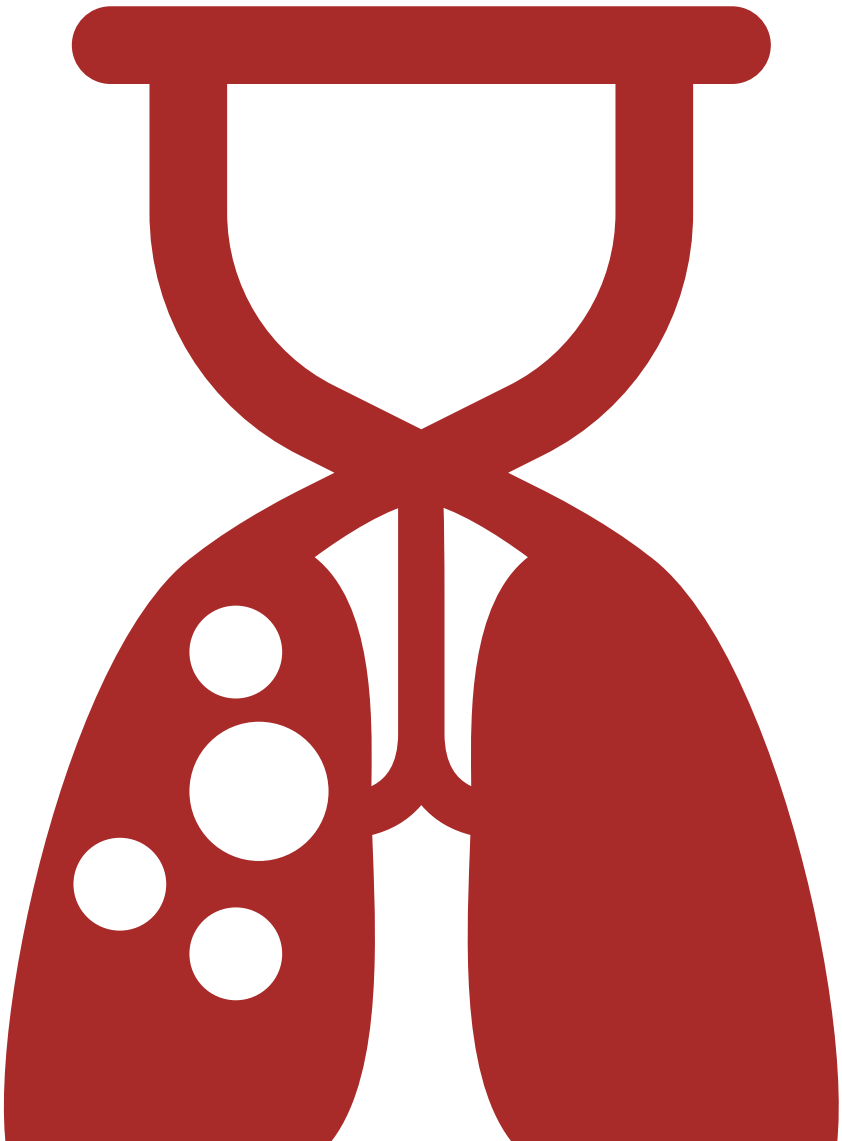
Abstract

In October 2022, the Russian Federation is required to present its seventh periodic report to the International Committee on Economic, Social, and Cultural Rights, including information on the implementation of earlier recommendations issued by the Committee concerning the prevention, treatment, and care of tuberculosis in individuals with comorbid HIV infection and drug dependency. In the present report, the authors analyze tuberculosis in Russia as of August 2022. They conclude that individuals with comorbidities remain in the highest-risk group for tuberculosis, including drug-resistant types, treatment for which has a greater duration compared to common, drug-responsive tuberculosis. Tuberculosis remains a primary driver of early mortality among those living with HIV. The authors offer practical steps that will enable rapid and effective progress in the implementation of the Committee's recommendations.



Introduction

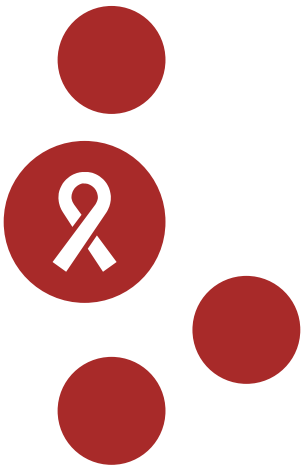
In October 2017, the International Committee on Economic, Social, and Cultural Rights[1] reviewed the sixth periodic report of the Russian Federation. Among the various issues with implementation of the International Covenant on Economic, Social, and Cultural Rights,[2] the Committee expressed concern about violations of Article 12 of the Covenant (right to health) associated with the spread of HIV infection, hepatitis C, and TB in Russia, particularly among people who use drugs. The Committee reiterated its previous recommendation to approach the issue from the perspective of protecting the human rights of individuals suffering from drug dependency (*see* E/C.12/RUS/CO/5, Item 29). The Committee recommended that the Russian Federation implement the following measures for the effective resolution of the aforementioned issues:

- Consider abolishing criminal liability for possession of drugs for personal use;
- Implement awareness campaigns to bring attention to the serious health risks associated with drug use;
- Combat discrimination against individuals suffering from drug dependency, including in their access to medical care;
- Provide individuals with required medical care, psychological support, and rehabilitation services, including legalization of effective treatments for drug dependency, such as opioid substitution therapy;
- Adopt programs to reduce physical harm, such as needle and syringe exchanges, and provide for their access, especially in correctional facilities, to combat the spread of TB, and support nongovernmental organizations providing such services, as was noted during discussions;
- Eliminate the root causes of the rapid, intensive growth of HIV and the spread of TB and hepatitis C, including by legalizing measures for HIV prevention among people who inject drugs in accordance with recommendations of the World Health Organization, the Joint UN Programme on HIV/AIDS, and the UN Office on Drugs and Crime, as well as by means of expanding the reach and distribution of medicines and medical services, such as antiretroviral therapy.[3]

In 2010 and 2013, the UN Human Rights Council Special Rapporteur on the right to health alerted the Russian Federation government to serious problems with the prevention and treatment of TB in people with comorbidities such as HIV infection and drug dependency in Russia. The Russian authorities failed to enact required measures to improve these problems, but instead have acted against the individual who filed a complaint with the Special Rapporteur, triggering this alert.[4]

The Russian Federation is required to present to the Committee its seventh periodic report by October 31, 2022. This report must contain information on implementation of the recommendations from the Committee on the Right to Health, including issues concerning TB in populations with comorbid HIV infection and drug dependency.

In this review, the authors present data on TB among individuals with comorbidities, including data on alarming trends in the development of drug-resistant forms of TB and the role of ineffective systems of treatment for drug dependency in the spread of the TB epidemic in Russia. These numbers can be a source of information for informal reports submitted by civic organizations to the Committee to improve the dialogue between the Russian Federation and the Committee. Such findings can also be a basis for more effective implementation of the Russian Federation's obligations under the International Convention.

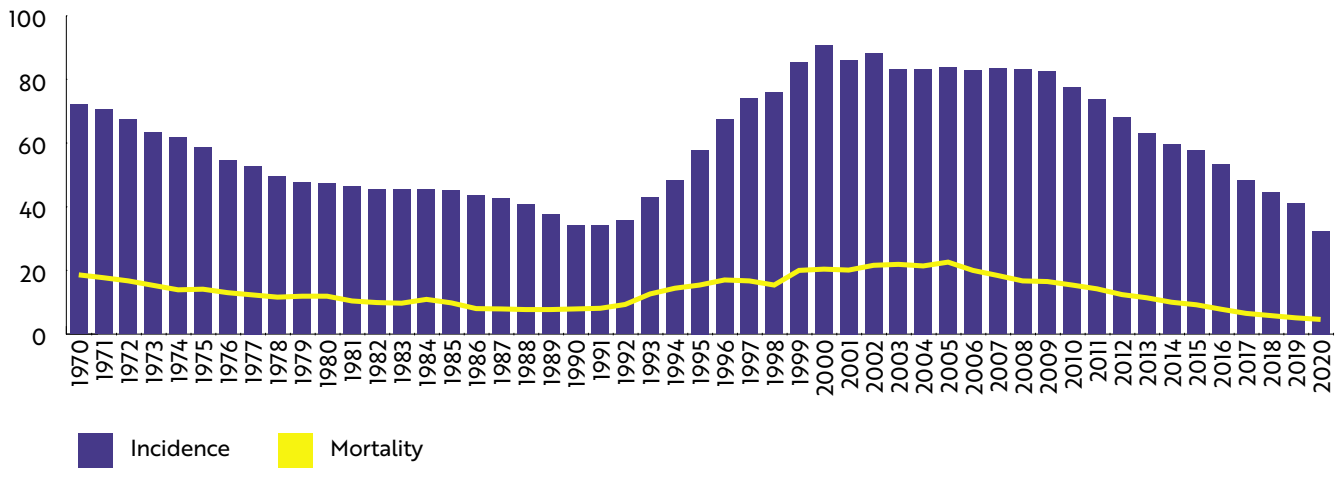


TB infection, including drug-resistant types, in Russia and the world

The many years spent combating TB have led to a decrease in the number of patients in Russia, which fell to 127,000 in 2019. However, numerous factors hinder the burden of TB from being further reduced. Prior to 2020, decreases in the overall incidence of TB infection occurred against the backdrop of improved preventive screening and a decrease in the proportion of advanced cases of TB found in new patients. In 2021, the overall incidence of TB infection decreased by 13.3% (from 44.4 cases per 100,000 people to 31.1) compared with 2018, and decreased by 54% (from 85.1 cases per 100,000 to 49.5 cases per 100,000) compared with 2008.[5] However, despite the substantial decrease in the incidence of TB in 2020, in 2021 this decrease continued at the same time as a clinical aggravation of TB — an increase in the rate of new TB infections featuring deterioration of lung tissue, massive bacterial discharge, and fibrocavernous TB.[6] The percentage of patients diagnosed with TB during healthcare visits has increased. This can be ascribed to delayed diagnosis of TB patients in 2020 during restrictions related to the COVID-19 pandemic.

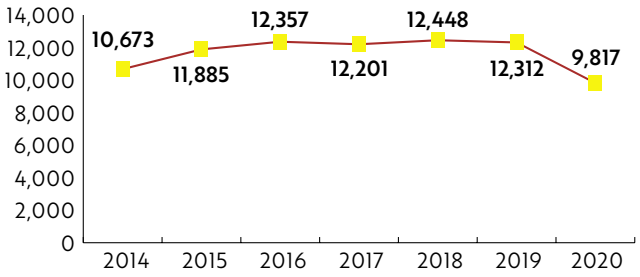
Today, in Russia, TB is contracted primarily by individuals between the ages of 18 and 44, with peak incidence occurring from age 35 to 44. Men make up 68.2% of new TB infections, which is consistent with global statistics.

TB incidence and mortality per 100,000 people in the Russian Federation, 1970-2020.[7]

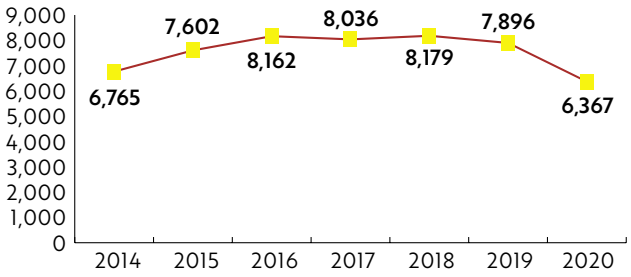


TB/HIV and MDR-TB in the Russian Federation, 2014-2020

Incidence of TB/HIV in the Russian Federation



Incidence of MDR TB



Prior to 2019, the percentage of individuals living with HIV who were newly diagnosed with TB rose on an annual basis, from 6.5% in 2009 to 24.7% in 2019.[8] In 2020, a substantial decrease occurred: there were 9,817 TB cases versus 12,312 in 2019. For 2019, the incidence of TB infections in patients with HIV was 61 times higher than the Russian average.[9] According to the Federal Registry of TB patients, nearly half of all individuals infected with TB and living with HIV have a drug-resistant type of TB.

The highest incidence of TB with comorbid HIV infection are noted in the following federal districts, regions, and territories: Urals (18.1 per 100,000 people), Siberia (24.3), Privolga (9.9), Irkustk (24.7), Kemerov (39.7), Novosibirsk (28.6), Samara (18.8), Sverdlovsk (23.0), Tomsk (22.4), Tyumen (23.0), Altai (23.5), Krasnoyarsk (18.4), and Perm (23.4).

Despite the progress and free access to treatment, TB continues to be the leading cause of death in people living with HIV in Russia.[10] In 2019, 19,168 TB patients enrolled in dispensary treatment died in Russia. Of that number, 7,822 (40.8%) were also living with HIV. The individuals who are dying are largely of working age (35-54 years), both men and women.

Globally, in 2019, approximately 206,030 individuals were diagnosed with and received treatment for rifampicin-resistant MDR-TB (MDR/RR-TB), an increase of 10% higher from 2018 (186,883 individuals). Despite these results, the TB situation in Russia is considered critical. A WHO assessment found that approximately half the cases of MDR-TB worldwide occur in three countries — India, China, and the Russian Federation.[11] Rates of successful treatment have declined rapidly as drug-resistant strains have increased worldwide.

Official statistics on patients with TB and comorbid drug use do not exist. Simultaneously, various data sources indicate that people who use drugs constitute up to 70% of people living with HIV who are in treatment for TB.[12]

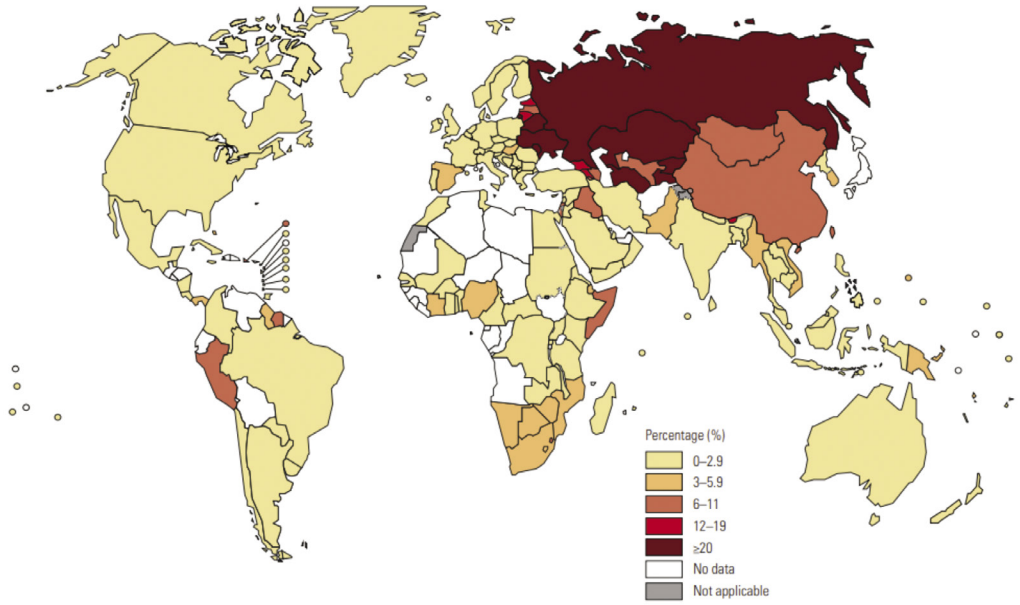
Parenteral transmission (69.4%) remains the primary route of HIV transmission among those co-infected with TB/HIV.[13] Although sexual transmission of HIV remains the dominant route, the proportion of people who use drugs among patients with comorbid HIV and TB has seen almost no decrease. In 2000, people who use drugs made up 76% of patients with comorbid pathologies of HIV and TB; in 2019, this was 69.4%.[14]

Overall, Russia the epidemic in Russia is improving, but the high level of MDR-TB (31.5% among newly diagnosed patients), the spread of HIV, and the increase in the risk of comorbid TB/HIV infection (25.6% among new and recurrent TB cases) will have a negative impact on the situation. Increased HIV transmission will hinder TB reduction and lead to growth in mortality among patients in many Russian Federation regions.

As a result, priorities in the country include TB prevention measures that have been proven to reduce TB incidence. One such measure is the battle against TB with comorbid HIV infection. The spread of HIV in Russia is already having a significant impact on the TB epidemic. The next priority is the refinement of diagnostic methods and treatment of MDR/XLR-TB. Reducing the spread of MDR-TB will require concentrated efforts within the entire national healthcare system and the modernization of tuberculosis treatment in response to the specific medical needs of such patients.

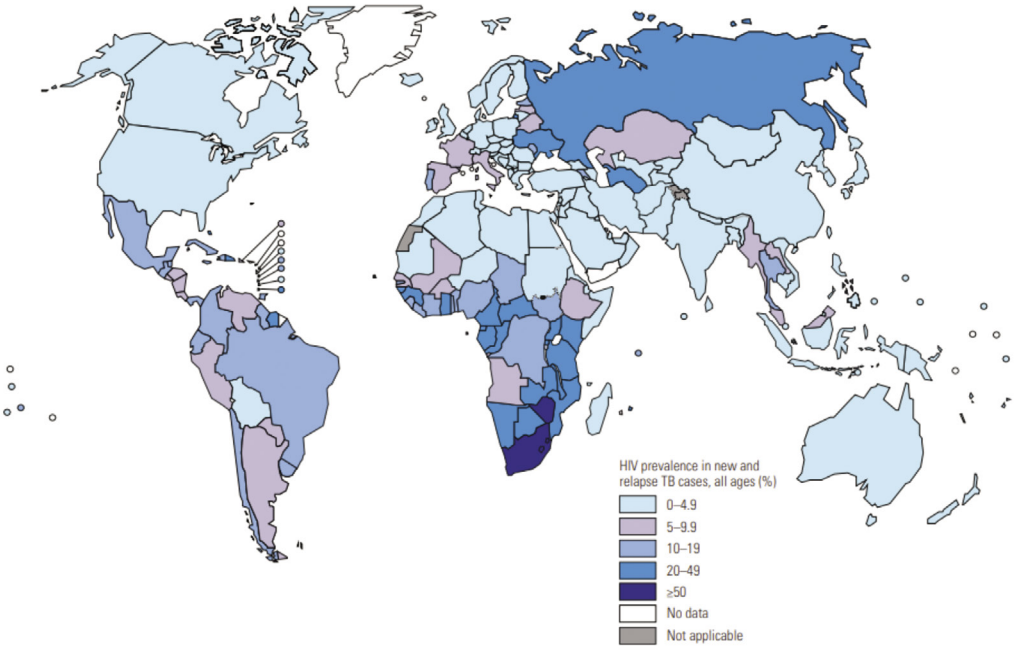
Treating MDR-TB requires extended courses of therapy using expensive and toxic medications, pathogenic exposure, and, often, use of advanced surgical and endoscopic treatments. Ensuring the administration of antituberculosis medications over an extended period of time (up to 20 months) is essential as are psychological and social support, follow-up care, and rehabilitation in specialized facilities. Currently, in accordance with international trends, Russia is starting to introduce new, abbreviated treatment regimens, but as yet only a modest number of regions are taking part in these trials.

Percentage of new TB cases with MDR/RR-TB*



*Percentages are based on the most recent data point for countries with representative data from 2005 to 2020. Model-based estimates for countries without data are not shown. MDR-TB is a subset of RR-TB.

Percentage of HIV infections among new and recurrent TB cases, 2019 (Global TB report 2020)



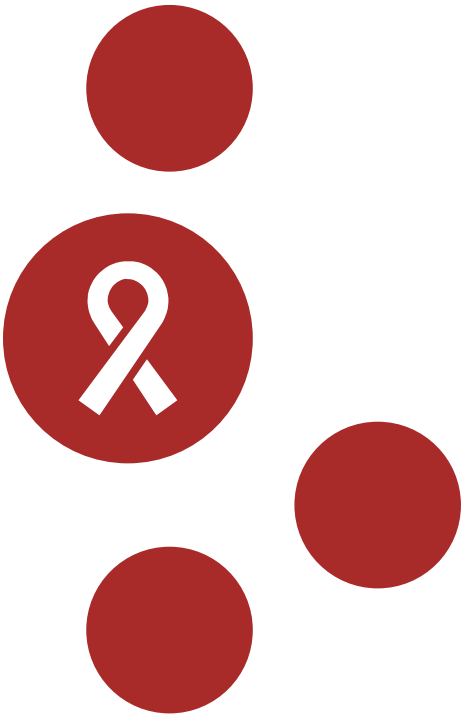
The MDR/XDR-TB epidemic amid treatment access issues for patients with triple diagnoses of dependency/HIV/TB

TB is an infectious (transmissible) disease that develops when the *Mycobacterium tuberculosis* (MBT) bacteria enters the human body. While it can affect any human organ, it most frequently ravages the lungs. Coughing, sneezing, and spitting by patients with pulmonary TB expel bacteria into the air. Transmission to others requires inspiration of only a small amount of such bacteria. Once that happens, tuberculosis infection (TBI) can develop. The term TBI indicates that the asymptomatic patient is infected with TB mycobacteria but has no clinical, laboratory, or x-ray evidence of active TB. The majority (70-90%) of those exposed to MBT will not be infected. However, the remaining individuals (10-30%) will develop TBI. The highest risk for developing active TB is during the first two years after exposure.

The known risk factors for development of active TB include: a condition or illness suppressing the immune system, such as HIV; use of various psychoactive substances, or tobacco; being underweight or having diabetes, peptic ulcer, chronic bronchial/pulmonary illnesses, etc.

In people living with HIV the annual risk of developing TB is 5-10% after contact with TB, while the risk for HIV-negative people is 5% over the first 5 years[15] and 5% for the remainder of their lives. Thus, people who use drugs and live with HIV are the group at highest risk for developing TB.

Clearly, people who use drugs are at increased risk of HIV, viral hepatitis, and TB than other people and are frequently harder to reach by epidemic response measures enacted at national or municipal levels. There are effective means of prevention and treatment of socially significant illnesses among people who use drugs, but insufficient investment in resources (financial, human, and material) often makes them inaccessible. The current situation is the result of multiple causes, including criminalization, stigma, discrimination against people who use drugs, and violations of basic human rights.[16]



Development of DR/MDR/XDR TB

Drug resistance is the ability of a bacteria to remain active despite exposure to medications. This means that the bacteria has a decreased sensitivity to the medications that would normally kill it, allowing it to multiply despite regular therapeutic doses.

Classifications of mycobacterial (MBT) drug resistance[17]:

Monoresistant:
MBT resistant to one antituberculosis agent

Polyresistant:
MBT resistant to two or more agents, but not to combination isoniazid and rifampicin (primary first-line treatment for sensitive TB)

N-resistant TB:
MBT resistant to at least isoniazid, but not to combination isoniazid and rifampicin

R-resistant TB:
MBT resistant to at least rifampicin

Multidrug resistant (MDR):
MBT resistant to combination isoniazid and rifampicin regardless of resistance to other antituberculosis agents

Pre-extensively drug resistant (Pre-XDR):
MBT resistant to rifampicin, with or without resistance to isoniazid, and resistant to any fluoroquinolone

Extensively drug resistant (XDR):
MBT resistant to rifampicin, with or without resistance to isoniazid, and resistant to any fluoroquinolone and to at least linezolid or bedaquiline

Each subsequent resistant variant is usually more difficult to treat; however, it is important to note that an effective therapy regimen has been developed for each type.

The mutation of the bacteria to resist antituberculosis agents is reinforced genetically, which means it becomes coded into the cells. Unfortunately, this is irreversible; sensitivity to therapies cannot be restored. This is a serious problem for efforts to curb the spread of MDR-TB and XDR-TB worldwide.

MBT drug resistance develops as a result of one or several of these chromosomal mutations within independent genes. Current scientific data show that the likelihood of MDR occurring because of spontaneous (natural) mutations is practically impossible, while each new mutation does not affect the sensitivity to different medicines.

The rise of MDR-TB in Russia is caused by delayed diagnosis of primary drug resistance, inadequate therapy regimens, insufficient dose administration and/or early treatment discontinuation, and treatment interruptions.

XDR and pre-XDR are the most complex types of resistant MBT to treat.

Risk factors for XDR-TB include primary MDR, two or more previous courses of pharmacotherapy, and administration of later-line ATT during previous courses of pharmacotherapy.

The following theories attempt to explain what risk factors influence the development of MDR-TB in patients with HIV:

1. Pharmacokinetics of ATT, including drug-drug interactions.[18] Some antiretroviral therapies may decrease the efficacy of ATT. ARV reduce uptake of pharmaceutical agents and increase the likelihood of malabsorption (disruptions in digestion of nutrients) associated with HIV and opportunistic infections affecting the gastrointestinal tract.[19]

2. Highly viable MBT strains are more common among patients living with both HIV and TB, which leads to more rapid accumulation of mutations in response to the active multiplication of the mycobacterial pool.[20] This is an important distinction in the development of illness in individuals with both MDR-TB and HIV versus those without HIV.

3. Social deprivation among patients living with HIV also affects therapy adherence.[21,22]

All of these theories seem fully rational; however, it has been shown that patients coinfected with HIV and TB more significantly differ from TB patients without HIV in the rate of primary rather than secondary MBT drug resistance.[23,24]

The risk of contact with patients having drug-resistant TB in medical and correctional facilities likely plays a significant role in the correlation of MDR-TB with HIV. According to molecular genetic research conducted on wastewater from workplaces of various medical organizations, there is extensive circulation of the MBT pathogen in one of the AIDS Centre clinics. Indeed, the most contagious individuals are TB patients who don't yet know of their illness and do not receive specific treatment (it is precisely these types of comorbid patients that visit the AIDS Centre). Patients with comorbid HIV and TB expel MBT more frequently and at a higher concentration than TB patients who don't live with HIV.[25,26] Another study investigating MBT viability (in terms of speed and extent of spread) in HIV-positive patients with disseminated pulmonary TB (TB that has spread beyond the lungs) demonstrated the predominance of a pathogen with high viability and more significant bacterial discharge, which makes it more easily transmissable.[27] In patients with comorbid infections, decreases in CD4+ lymphocytes, which play a key role in immunity to tuberculosis, are accompanied by increased multiplication of MBT in the lungs and dissemination of the pathogen. Accordingly, patients with HIV infection develop disseminated and generalized TB much more frequently than do those patients infected only with TB.[28]

Sharing psychoactive substances also brings a high risk of exposure to MBT. People living with HIV develop illness shortly after infection with MBT due to a decreased initial immune response. After exposure to MBT, people living with HIV are at very high risk of developing TB within two years, especially if they also use drugs.

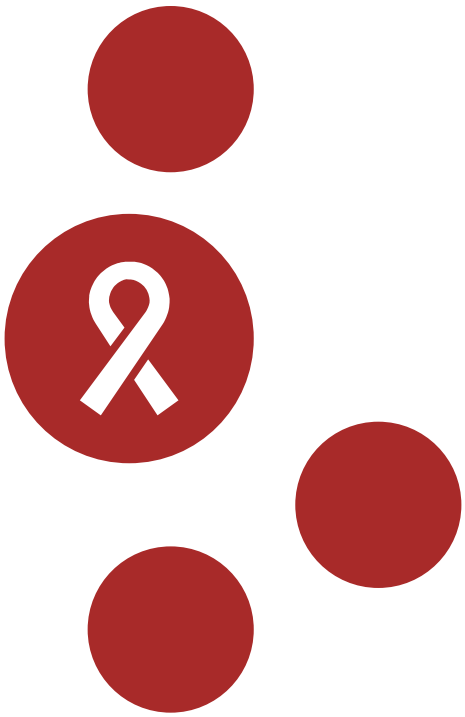
Five pharmacotherapeutic regimens are used to treat TB. Pharmacotherapeutic regimens are prescribed based on an individual determination of the pathogen's drug resistance. Treatment consists of an intensive phase and a continuation phase. Basic principles of TB treatment in people living with HIV do not differ from those governing treatment of other patients, and depend upon the sensitivity of the MBT to pharmaceutical agents. Concurrently, it is always necessary to consider drug interactions with antiretroviral therapies (ART). Comorbid HIV and TB infections requiring dual therapies (ART and ATT) increases the risk of treatment interruption or refusal. Treatment of patients living with HIV must also consider immune reconstitution inflammatory syndrome as a factor affecting the condition of patients beginning treatment for TB and the adherence to such treatment.

The Russian TB treatment system

Medical assistance is provided to patients with TB in accordance with Order No. 932n, *Provision of Medical Assistance to TB Patients*, issued November 15, 2012, by the Russian Ministry of Health.

After diagnosis, the TB patient is registered with antituberculosis services. After registration, the healthcare system typically responds quickly and precisely, especially regarding TB with bacterial discharge. All cohabitating and coworking contacts are tested. Patients are asked to provide other close contacts, who will be invited to test. The patient can decide whether to inform their close contacts about their illness or provide contact information to medical authorities. Patients with HIV/TB/drug dependency comorbidities may have many contacts; it is not known how many of these contacts are tested in a timely manner and begin treatment for TB infection.

A medical commission determines where a patient will begin treatment. There are several types of facilities: a 24-hour tuberculosis inpatient clinic; a day-patient clinic; a TB therapeutic centre; an outpatient clinic. If the patient has no bacterial discharge, has limited TB activity, and has no serious comorbid illnesses, treatment may be on an outpatient basis.



Indications for hospitalization in a 24-hour inpatient setting may include both medical and nonmedical factors, as well as any combination of such:

Medical factors:

- Patient has bacterial discharge; i.e. sputum contains MBT[29];
- The patient has complications of TB, regardless of whether MBT discharge is present;
- Moderate or severe TB, regardless of bacterial discharge;
- Severe adverse reactions to ATT requiring treatment not possible on an outpatient basis, regardless of bacterial discharge;
- Presence of moderate to severe concomitant illnesses.

Nonmedical (social) factors:

- Epidemiological factors, such as residence in communal apartments, dormitories, or apartments with newborn and other minor children or pregnant women;
- Circumstances that may reduce patient adherence to treatment (such as use of psychoactive substances);
- Lack of adherence during outpatient treatment as determined by medical commission.

Decisions on the duration and structure of treatment in individual cases are made by medical commission and depend upon clinical, bacteriological, and social factors. Extensions of inpatient treatment are determined in consideration of the aforementioned factors.

Inpatient tuberculosis treatment in Russia is currently more common than outpatient services, which is out of step with modern treatment requirements.[30] Treatment of TB is provided by the government at no cost to the patient.[31] Courses of treatment may be administered either in a hospital or outpatient setting (receiving medication at a tuberculosis dispensary). The intensive phase of treatment is most commonly administered in a hospital. Treatment

during this period usually results not only in the cessation of bacilli discharge (i.e. the patient ceases to discharge bacteria, although not all patients may have started to discharge bacteria before the treatment), but also in the selection of an appropriate plan and achievement of initial positive results. As a rule, after completion of the intensive phase, the patient is discharged and placed under the care of a tuberculosis specialist to continue treatment at home. In some cases, day-clinic care is recommended — daily visits to a dispensary and administration of medications in the presence of a nurse, with video monitoring — or home administration of medications, but also under observation of medical personnel by means of video link or home visits.

The minimum duration of treatment for TB is six months. Such a duration of treatment will be determined in cases where a patient has a limited type of TB with no bacterial discharge and which retains sensitivity of primary, first-line tuberculosis therapies. All other situations — disseminated TB, bacterial discharge, drug-resistant TB types, comorbid illnesses — extend the duration of pharmacotherapy. Some courses of treatment may continue for up to 20 months.

A full course of treatment is provided in day clinics to patients with pulmonary TB who are treatment adherent, whose respiratory systems show no deterioration, who have no bacterial discharge, and who are in satisfactory physical condition.

Treatment in day clinics has certain limitations:

- The illness should be asymptomatic or mildly symptomatic;
- Comorbid illnesses should be mild or absent;
- Adverse reactions to ATT can be resolved without hospitalization;
- Patients with active TB should not cohabitate with children or adolescents;
- Patients should not have exacerbating social factors and should be adherent to treatment.

In addition, all patients who have completed the intensive phase of treatment may continue treatment at day clinics, provided that, by the decision of a medical commission, they have no medical, social, and/or epidemiological indicators requiring further inpatient treatment. Such patients receive monitored treatment in day clinics for the duration of the continuation phase, or on a partial basis alternating with treatment in a therapeutic centre.

Patients who successfully complete the intensive phase of pharmacotherapy may continue treatment in TB therapeutic centres. In the event a patient demonstrating bacterial discharge refuses hospitalization or treatment in a day clinic, monitored treatment may be administered at home by means of mandatory daily visits by medical personnel. Outpatient treatment in the continuation phase is administered in TB dispensaries, which lack day clinic facilities.

After completion of the primary course of treatment and the elimination of all clinical, radiological, and microbiological indicators of active TB, as confirmed by physical examination, the patient is considered clinically cured and transferred to a group with less intense dispensary care for follow-up care and rehabilitation.

The success of treatment for HIV infection and TB should be determined not so much by clinical and laboratory indicators in carefully selected patient groups, but rather by the ability of medical and nonmedical specialists to reach and treat people living with HIV who have been marginalized by society.

Civilian and prison TB treatment systems and the drug-resistant TB epidemic

Providing uninterrupted TB treatment in prisons and other detention facilities is essential to reducing fatal outcomes, development of drug resistance, and further MBT transmission. Treatment should follow prisoners in all stages of their detention, including pretrial detention, prison transfers, and post-release.[32]

In Russian correctional facilities, 53.8% of patients are diagnosed within days of entering detention and being routinely tested, which demonstrates the inadequacy of TB detection in high-risk social groups.[33]

A study conducted in 2019, *Medical Care for Tuberculosis-HIV-Coinfected Patients in Russia with Respect to a Changeable Patients' Structure,* analyzed the social characteristics of patients with HIV who were also diagnosed with TB: unemployed, working age, people without disabilities — 80.2% of patients; people with disabilities — 13.3%; unhoused — 4.1%; previously incarcerated — 53.7%, of whom 57.1% were incarcerated for terms greater than three years.[34]

According to official statistics, the number of newly diagnosed TB patients in Russian Federal Corrections Service (RFCS) facilities has decreased steadily and linearly on an annual basis; the COVID-19 pandemic has had no significant impact on diagnosing TB patients in correctional facilities.[35] The percentage of RFCS inmates with new TB infections decreased from 7.6% in 2018 to 7.3% in 2019.

A considerable obstacle to uninterrupted TB treatment in patients released from correctional facilities is the lack of follow-up between RFCS medical services and the civilian sector. Tuberculosis therapists note cases in which the transfer of RFCS medical documentation is delayed and contains incomplete information about patients' conditions and treatment stages.

According to charitable organizations tracking this group of patients, patients do not trust the medical services they received during incarceration. Patients in the prison system receive few consultations from medical and nonmedical specialists, no education on TB treatment, and have no care or support programs.

Inaccessibility of effective TB treatment for patients with drug dependency and its role in the drug-resistant TB epidemic in Russia

Globally, people who use injection drugs are disproportionately vulnerable to HIV infection. People who use injection drugs also have an increased risk of TB infection compared with the overall population. The link between TB and drug use is primarily associated with injection drugs, but people who use crack cocaine and opium are also at increased risk of TB infection.[36]

Efficacy of treatment for TB patients globally and in the Russian Federation compared with European and worldwide statistics:

Patient category	Indicators of efficacy*		
	Russia	World	Europe
New and recurrent cases	69%	85%	75%
Previously treated	48%	71%	57%
MDR/RR-TB	55%	58%	59%
TB/HIV coinfection	44%	76%	52%

To end the epidemic, efficacy of treatment for TB patients must equal or exceed **85%**.** Efficacy of treatment for patients with MDR-TB must equal or exceed **75%**.***

**Global TB Report 2020*

***Road map to prevent and combat drug-resistant tuberculosis, Regional Office for Europe, WHO, 2011*

****Global strategy and targets for tuberculosis prevention, care and control after 2015, WHO, 2013*

As shown in the table, treatment efficacy in Russia for each patient type is below what is required to end the TB epidemic. Among patients coinfected with HIV and TB, efficacy is particularly low; this is also undoubtedly affected by the fact that at least 60-70% of these patients also have drug dependency. Issues facing people who use psychoactive substances are key in diagnosis, prevention, and treatment of TB. Without question, those key issues include the high level of stigma attached to people who use drugs in society, self-stigmatization, and constant fear of criminal prosecution. The community is extremely closed, and as a rule people who use drugs do not seek medical assistance promptly. Workers in the tuberculosis therapy service lack the experience and knowledge required to work with people living with HIV who use drugs. Programs designed to diagnose, prevent, and treat TB have no low-threshold, unimpeded access to them. **People from highly stigmatized and disadvantaged groups, which can include people with drug dependency and HIV, often lack documentation; due to the lack access to evidence-based drug dependence treatment, these people can demonstrate weak adherence to ART; due to their overall poor health condition, they can ignore TB symptoms; TB clinics can discharge them from treatment programs for drug or alcohol use or other similar types of protocol violations; and if taken for outpatient therapy, these people may fall out of treatment due to unstable lifestyle during relapses into illicit drug use.** Patients who are socially isolated will often not seek medical assistance even in emergencies, which precludes early diagnosis and decreases the likelihood of successful treatment.

Counseling about TB is given little attention in existing HIV-prevention programs. According to a 2022 survey of community-focused civic organizations about their experience in the prevention, diagnosis, and treatment of TB, as well as of HIV/TB coinfection,[37] 100% of respondents required additional education on TB issues. The survey was taken by personnel from 32 organizations in 20 different regions of the country. People living with HIV (95%) and people who use drugs (90%) are among the groups with which employees of non-profit organizations work most often. Fifty-eight percent of those surveyed provide counseling on TB prevention. Somewhat fewer (50%) provide counseling on TB diagnostics. Fewest of all were consultations on TB treatment adherence (37.5%) and TB treatment (22.5%). In other words, non-profits play a small role in supporting patients with HIV and drug dependency during TB treatment. Among employees of HIV-service non-profits, it is believed that TB can be treated only on an inpatient basis, although for patients with drug dependency video monitoring or home care are excellent replacements. Experience with implementing patient-oriented plans has shown that they work. Among patients on the verge of early treatment interruption included in the "Sputnik" project that was conducted in the Tomsk region, adherence rose from 59.8% to 78.5%.[38] Adoption of patient-oriented approaches led to an increase in TB patient adherence to 87.1%.

According to statements from drug-dependent patients living with HIV, a TB diagnosis is a serious blow to their mental health. Among this group of patients, there is a strong mistaken belief that TB is incurable and inevitably fatal. The connection between this belief and mental health issues for people diagnosed with TB is obvious. For example, in Kazakhstan, depression was diagnosed in 50% of patients with MDR-TB at the start of treatment. During treatment, depression developed in another 18%, while 11% of patients experienced anxiety disorders.[39] Approximately half of patients with protracted psychiatric illnesses have alcohol and drug use or drug dependency in their medical histories.[40] More than 50% of people with problematic drug dependency have concomitant psychiatric disorders.[41] Of those, 26% have affective disorders, such as depression or bipolar disorder; 28% have anxiety disorders. During TB treatment for people living with HIV and who use drugs, special attention should be paid to mental health issues. Psychosis is a possible adverse reaction to TB treatment. In light of rapidly changing drug trends, it is critical to consider drug interactions between ATT and various controlled substances in order to avoid severe adverse reactions. In other words, medical personnel should have the skills necessary to counsel patients who use drugs. In practice, such patients do not receive any kind of treatment for problematic substance use. Even withdrawal syndrome goes untreated in tuberculosis inpatient facilities, leading patients to continue to use psychoactive substances in hospitals or discharge themselves from facilities. Notably, Order No. 135n, *Specialized Medical Care for Withdrawal Syndrome Caused by Use of Psychoactive Substances,* issued September 4, 2012, by the Russian Federation Ministry of Health, provides for prescription of tramadol to relieve acute withdrawal symptoms during inpatient treatment for a period of 10 days. Order No. 124n, *Primary Health Care for Withdrawal Syndrome Caused by Use of Psychoactive Substances,* issued September 4, 2012, by the Russian Federation Ministry of Health, likewise provides for prescription of tramadol to relieve acute withdrawal symptoms during outpatient treatment for a period of 10 days. However, such prescriptions are not provided anywhere in Russia aside from the Kaliningrad region.[42]

Concurrently, treatment for TB and drug dependency is critically important for people living with HIV. Without access to such treatment, patients may die from TB or overdose. Research conducted into causes of mortality among HIV/TB[43] patients in five regions of the Russian Federation shows that fatal outcomes have no link to TB in half of cases. Among the most frequent causes of mortality are several secondary infections, such as wasting syndrome — 19.7% of cases; other secondary infections — 27.1%; cirrhosis of the liver resulting from hepatitis C or alcoholism — 18.7%; drug overdose — 12.3%; or accidents — 4.6%.

Given the prohibition on supportive therapy using opioid agonists and the pervasive lack of drug dependency treatment in antituberculosis service facilities, the situation with lack of access to treatment is becoming ever more tragic. Patients with the comorbidities of HIV/TB/drug dependency are limited in terms of access to medical services, frequently become unfit for work, and find themselves without means to support themselves. They have nowhere to live, nothing to eat, and cannot provide for their own daily needs. They depend on the charity of relatives to survive. Such cases require comprehensive support services.

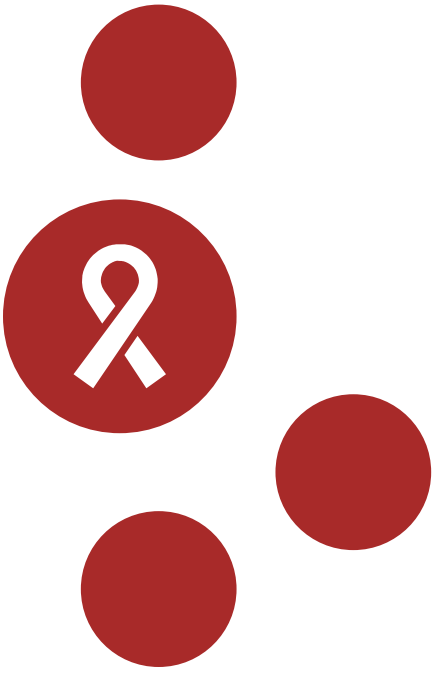
Issues with access to medical assistance for people who use drugs affected by the HIV/TB epidemic during COVID-19.

Assessments of TB epidemiology are essential for providing and refining tuberculosis treatment. Such assessment took on special importance in 2020-2021 when the Russian Federation, like many other nations, was forced to enact measures to suppress the spread of COVID-19.[44] These measures led to changes in people's daily lives and had a substantial impact on the medical system, including TB treatment. As part of social support measures, pensions and benefits were paid in lump sums. This averted a pronounced reduction in living standards, something that would negatively affect TB epidemiology.[45] Such support measures were practically inaccessible to people who use drugs, who frequently lack of identification documents, making it impossible to register for government assistance and benefits.

In 2020, Russia adopted temporary best practices to provide tuberculosis treatment during the COVID-19 pandemic.[46] These recommendations include measures essential for reducing the negative impact of COVID-19. Recommendations to reduce the duration of inpatient treatment and expansion of outpatient treatment, implementation of remote patient consultation in all phases of treatment, and implementation of online remote treatment monitoring from inpatient facilities all deserve special mention. The development of replacements for inpatient approaches to TB treatment may help with treatment adherence among those living with HIV/TB/drug dependency. These successful practices should be implemented in tuberculosis facilities across the nation.

In some regions, non-profit organizations have delivered tuberculosis and antiretroviral medications to patients at their homes.

An analysis of deaths caused by TB in 2020-2021 shows that, despite the response of the medical system to the pandemic, there is nevertheless an increase in the number of residents in whom TB was detected posthumously. This increase — 847 deaths — brings Russia back to 2016 levels. (Recent yearly totals are as follows: 2015 — 1,011 deaths, 2016 — 836 deaths, 2017 — 723 deaths, 2018 — 748 deaths, 2019 — 749 deaths, 2020 — 792 deaths, 2021 — 847 deaths). The percentage of new cases of TB in residents that were detected posthumously rose from 1.7-1.8% in 2015-2019 to 2.7% in 2020 and 2.9% in 2021. These statistics dramatically attest to the worsening of TB detection in 2020-2021, which led to posthumous (increase in percentage of patients with posthumous TB diagnoses) and delayed (increase in percentage of TB patients deceased prior to observation year) diagnosis of TB infections.[47]

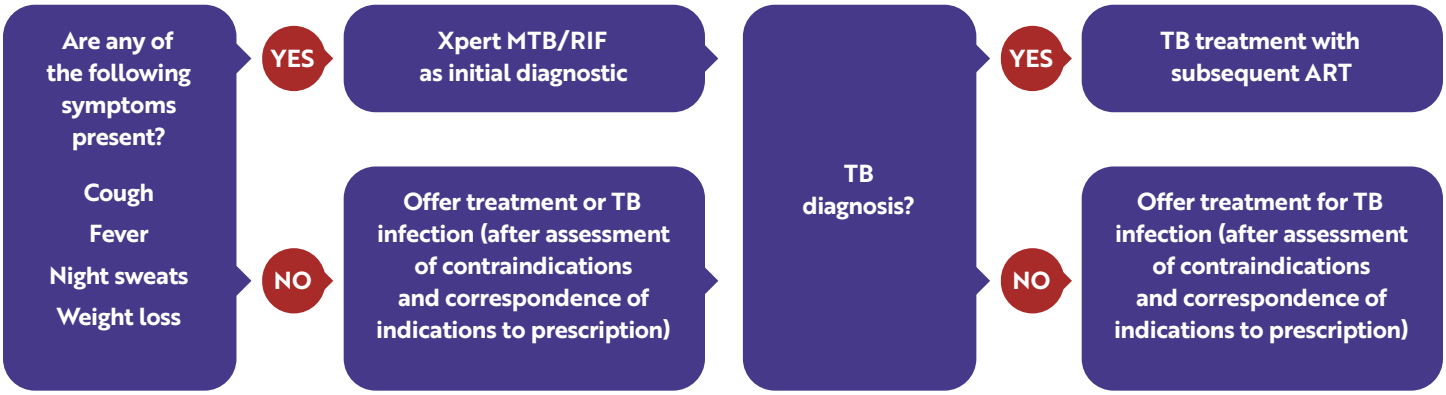


Recommendations for improving access to TB treatment for patients with drug dependency

Early access to ART and TB treatment

Personnel employed by non-government organizations (NGO) are frequently the first point of entry for people who use drugs into programs for the treatment, care, and support of HIV and TB patients, making it essential to take advantage of every possibility to provide counseling and testing for HIV and TB. NGO employees should be able to recognize TB symptoms and send patients to specialized medical facilities. Screening for TB in Russia should be accessible to people who use drugs, especially screening for drug-resistant TB types. People living with HIV should regularly undergo TB screening in accordance with WHO algorithms based on four symptoms. This screening determines whether active TB is present. In addition, this screening identifies those in need of further examination, diagnostics, and TB treatment where necessary. WHO recommends the use of Xpert MTB/RIF as the first test for active TB for all people living with HIV and for any individual in whom MDR-TB is suspected. Organizations providing support to people who inject drugs may offer access to early TB detection and prompt prevention of and treatment for TB and HIV. Therefore, it is critically important that employees of such programs are educated about the symptoms of TB.

A tool to screen for symptoms of TB in people who inject drugs and are living with HIV does not require expense. It can be used during counseling of living with HIV and drug dependency by both medical and nonmedical specialists.[48]



It is also recommended that systematic TB screening uses other methods, such as radiological exams of people who inject drugs but do not have HIV in countries with high TB burdens.

ART is currently the most effective strategy for reducing TB incidence among people living with HIV, regardless of CD4 cell counts; despite this fact, access to ART for people who use drugs remains disproportionately low. The accessibility of ART reduces the risk of TB infection among people living with HIV by 58-80%.[49] In other words, early initiation of ART is critical for preventing TB. Despite early initiation and extended administration of ART, TB incidence among people living with HIV remains high. Therefore, further interventions are essential to reduce this burden. One such intervention is the treatment of TB infection. Treatment of TB infection should be conducted in all people living with HIV without exception (adults, adolescents, children, including pregnant women [WHO 2020]), regardless of CD4 cell counts. Preventive treatment should be recommended after active TB infection is ruled out.

Educating society, non-profit employees, and medical personnel

It is essential to increase society's understanding of people who use drug and specialists who work with them in the prevention, diagnosis, and treatment of TB. People who inject drugs who receive the necessary support can successfully adhere to treatment regimens and achieve clinical results similar to those seen in non-drug users. Treatment adherence increases in response to direct observation of medication

administration, reminders, and peer counseling; with access to assistance during crises and financial incentives; and with measures to provide care, which include supportive therapy with opioid agonists and meet the health and psychological needs of people who inject drugs. Changes must be made to current approaches to prevention and treatment of HIV/TB that will consider the specific needs of people who use drugs. Patients should be sufficiently motivated to seek medical assistance promptly upon appearance of initial signs of TB, i.e. they must know the signs and pay attention to them. Community support for the treatment of TB and treatment adherence may play a leading role. Community organizations and networks are key to providing access to and engagement with TB services, as well as support for access to treatment and prevention services. Volunteer groups can provide emotional support to cope with additional difficulties associated with TB, including stigma and discrimination. They can likewise increase awareness about treatment and treatment adherence, as well as fight for the right of access to services for those who encounter difficulty getting help.[50]

Development of drug dependency treatment during TB treatment

It is important to increase knowledge of psychoactive substances and their impact on treatment among medical personnel. Active drug use and mental health problems should not be used as the basis for refusal of treatment. Knowledge of potential drug interactions is critical for effective treatment. Obviously, there is need for clinical research into drug-drug interactions between medications and psychoactive substances. The results of such research provide practical information; however, treatment should be individualized. Integration of HIV/TB treatment with addiction medicine is needed. To this day, there is a lack of specific information about treatment for TB and HIV among people who use drugs.

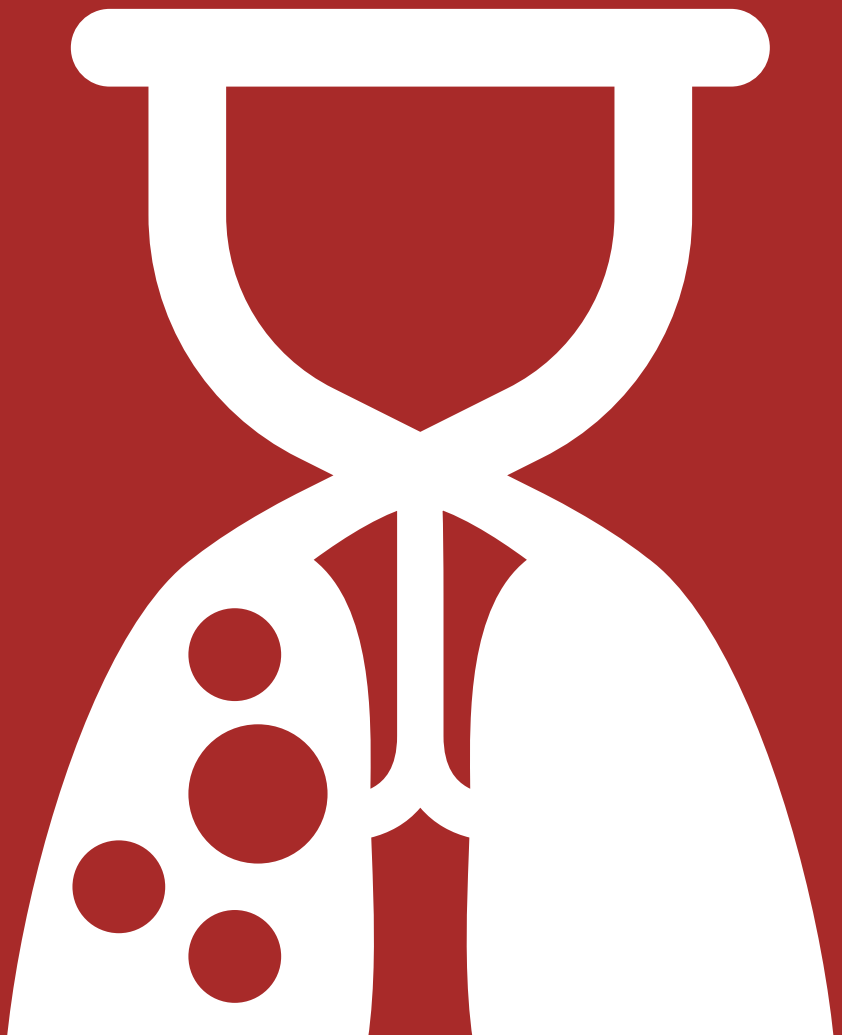
A description of treatment for patients who use opiates is provided as part of a project to gather and study best practices in treatment and clinical management of TB patients, including those with multidrug resistance and HIV coinfection.[51] Treatment of this group is complex and should be augmented with active psychotherapy. All medical personnel engaged in treatment of patients with drug dependency require constant consultation about treatment adherence issues. Treatment of withdrawal syndrome is provided in intensive care units of tuberculosis inpatient facilities in accordance with accepted standards (pain relievers, sleep aids, antianxiolytics, neuroleptics, etc). Tuberculosis is not treated during treatment of withdrawal syndrome. The patient is subsequently transferred to the proper department for treatment of primary illnesses. At this stage, supportive medication is provided (antidepressants, sleep aids, antianxiolytics, etc), as are various rehabilitation services. After transfer from intensive care, medications are prescribed for the patient and administered and monitored by nurses. Treatment efficacy depends upon the patient's motivation and social and intellectual stability. An important aspect of treating patients with TB who use opiates is preventing deaths caused by opiate overdose. It is critical to have naloxone on hand in hospitals and in homes where outpatient treatment is provided. The quality of psychological and drug dependency care during TB treatment must also improve.

Replacement therapy is very frequently the basis for successful ART adherence. TB patients with opioid dependency need access to replacement therapy programs. According to the WHO consolidated guidelines, *Integrating collaborative TB and HIV services within a comprehensive package of care for people who inject drugs,* there is no need to wait for opioid withdrawal to initiate treatment for TB, hepatitis, or with antiretroviral therapy. In standard practice, psychosocial support should be provided along with pharmacologic treatment for opioid dependency. Preclinical research has shown a probability of significant drug-drug interactions between opioids and ART drugs. A number of ART drugs may independently reduce methadone concentrations and, depending upon individual characteristics, lead to withdrawal and increase the risk of relapse into opioid use.

In developing and implementing regulatory documents, health authorities should consider the experience and opinions of non-governmental organizations representing the interests of patients, of patient groups affected by TB and HIV, and of people who use drugs. Government should work to create a favourable environment for integration of services for people who use drugs.[52] Drug use should not limit access to modern approaches to TB treatment and use of abbreviated treatment regimens.

Conclusions

Effective countermeasures against TB, including MDR- and XDR-TB, are impossible without active efforts among patients with HIV coinfection and drug dependency. All necessary resources and technologies for such countermeasures are present in Russia. A restructuring of antituberculosis services and implementation of substantial cooperation with addiction services for the benefit of patients are not merely possible, but directly stipulated in current regulatory policies and by best practices. If implementation of replacement therapy using opioid agonists is banned by statute in Russia and requires changes to current law, the use of tramadol for relief of withdrawal syndrome is directly stipulated by current orders issued by the Russian Federation Ministry of Health. The recommendations of the Committee on Economic, Social, and Cultural Rights should be implemented by reforming legislation and law enforcement practices applicable to the drug trade. The recommendations presented herein can be implemented immediately as part of initial substantial steps toward acting on the Committee's recommendations.



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