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TB/HIV in the Russian Federation

Epidemiology, Peculiarities of Clinical Manifestations, and Treatment Outcomes

Moscow 2017

TB/HIV in the Russian Federation. Epidemiology, Peculiarities of Clinical Manifestations, and Treatment Outcomes

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TB-HIV has become one of the most significant medico-biological and social problems in the recent decades. Success in solving this problem is largely predetermined by well-being of the society and may serve a reliable gauge of efficiency of public health system and state social policy. That's what accounts for the attention from many researchers of various medical professions that is drawn to individual aspects of the problem.

The proposed monograph has a number of specific aspects and advantages in comparison to the majority of studies dedicated to TB/HIV issue. The major of the advantages is the huge amount of actual data, high professionalism, and creative approach to processing and analysis of the material. As a consequence, based on the analysis of available official reporting forms of Russian Federation and open sources of information (including WHO reports), authors not merely identify the presence of certain tendencies of epidemic process development but also analyze consistent patterns of the course of tuberculous process and its pathogenesis in patients with various manifestations of HIV-infection. Almost each chapter of the monograph may serve as a basis for an independent scientific research and provides profound factual evidence for specialists having interest in this problematics. The monograph may be recommended not only to the target audience i.e. phthisiologists, infectious disease specialists, epidemiologists and health administrators, but also to health professionals of other medical specialities as long as methods of scientific analysis used in this work are reliable, informative, effective and up-to-date.

Reviewer: Professor K.G. Puchkov, MD, PhD

Contents

List of Abbreviations

AFB – acid fast bacilli

ChT – chemotherapy

SIZO – pre-trial detention center

DR – drug resistance of MbT to at least one antituberculosis agent

DST – drug susceptibility test

ERTB – tuberculosis of extrarespiratory localization

FR – Federal region

HIV – human immunodeficiency virus

MbT – mycobacterium tuberculosis

MDR, MDR-TB – multidrug resistance of MbT, tuberculosis with multidrug resistance of MbT

OR – odds ratio

REPTB – respiratory extrapulmonary tuberculosis = tuberculosis of pleura, upper air tract, and intrathoracic lymphatic nodes

RR – rifampicin resistance

RTB – relapse of tuberculosis

RTB/HIV+ - relapse of tuberculosis associated with HIV-infection

RTB/HIV+ - relapse of tuberculosis without HIV-infection

TAF – treatment after failure

TB – tuberculosis

TB/HIV, TB/HIV+ – tuberculosis associated with HIV-infection

TB/HIV- – tuberculosis without HIV-infection

WHO – World Health Organization

XDR, XDR-TB - extensive drug resistance of MbT, tuberculosis with extensive drug resistance of MbT

Please, send your opinions and censorious remarks concerning the content of the monograph to E-mail address: sterlikov@list.ru.

Introduction

The problem of tuberculosis associated with infection induced by human immunodeficiency virus (HIV) becomes more and more urgent nowadays. According to WHO data, more than 500 thousand TB cases (new cases and relapse TB cases) associated with HIV-infection were registered in 2015. According to WHO estimates, 9.6 million people living with HIV died of tuberculosis over the period of 2005 – 2015 [11].

Tuberculosis associated with HIV infection is dangerous due to presence of a number of associated negative consequences such as a higher rate of multidrug- resistant tuberculosis, a relatively low treatment success rate in patients with HIV-associated tuberculosis; especially in economically developed countries. Thus, in the WHO European region, the proportion of patients (new cases and relapse TB cases) with TB/HIV who completed treatment successfully was only 41%, while among all patients (new cases and relapse TB cases) it was 76% [11].

These and other data published in the WHO Global Tuberculosis Report are based on information submitted for the Global Report by countries. Unfortunately, the Russian Federation was not among these countries down to recent times. It was prevented by the absence of required forms of statistical recording and, consequently, reporting. Official statistics data don't allow us to keep record of HIV-associated TB cases registered for treatment, and to analyze peculiarities of TB clinical forms, as well as results of microbiological diagnostics. We don't possess any reliable data on characteristics of the mycobacterum tuberculosis drug resistance in TB/HIV patients and their treatment outcomes. Moreover, we are not aware of drug resistance and treatment outcomes in patients with tuberculosis without HIV-infection, for instance, in relation to gender and age. It was decided to bridge a number of gaps in 2017. It became possible thanks to implementation of an electronic system of treatment cases registration that was carried out by leading specialists of organizational and methodological departments and offices of a number of antituberculosis institutions, which also made it possible to form respective teams for conducting the present research. For the sake of completeness, O.B. Nechayeva and other authors agreed to describe the whole epidemiologic picture on HIV-associated tuberculosis, both among the civil population and in penitentiary system. The present monograph is a result of consolidated efforts.

We hope that findings of the research will prove useful for the readers.

Chapter I

Epidemic process of tuberculosis associated with HIV-infection in the Russian Federation. Forecast of development

O.B. Nechayeva

In Russia, the majority of population is infected with Mycobacterium tuberculosis (MbT) already at an young age. Infecting with MbT occupies a central position in understanding the dynamics of tuberculosis epidemic in the society. Infection contamination reflects the volume of reservoir of tuberculosis infection across the population. The higher the rate of tuberculosis infection contamination across the population, the higher TB notification rate is.

Probability of being infected depends on the number of infected droplets («infectious cores») in a unit of air volume, i.e. on the density of infectious particles, as well as upon the duration of contact of a susceptible person with these contagious particles. The number of MbT found in sputum samples correlates with patient's contagiousness. Probability of being infected after contact with a source of infection decreases with decrease of closeness of contacts with the source of infection. The most effective means to lower patient's contagiousness is treatment of the patient. A patient with contagious form of tuberculosis, who does not receive any treatment, remains contagious for a longer period of time than a patient who is diagnosed and timely prescribed with adequate therapy.

Infection of MbT is an essential but insufficient condition for tuberculosis development. The risk of being infected is defined not only by external factors. The immune response of an organism is also of importance. Macrophage function may differ in different individuals thus influencing the risk connected with Mycobacterium tuberculosis implantation and its ability to bring on infection development. The risk of tuberculosis development in case if introduction of infection has already taken place is mainly of endogenous character and is defined by cellular immune system effectiveness.

In Russia, it turned out possible to significantly lower TB notification rate and prevalence rate in the recent years (Fig. 1.1-1.2). TB notification rate decreased by 41.0% (from 90.4 per 100 000 population in 2000 to 53.3 in 2016); rate of disablement due to tuberculosis decreased by 58.6% (from 74.6 per 100 000 population in 2001 to 30.9 in 2016); and TB prevalence rate decreased by 42.0% (from 209.1 per 100 000 population in 2005 to 121.3 in 2016).

Stabilization of tuberculosis epidemic situation in Russia is not characterized by steadiness primarily due to HIV-infection epidemic development and high TB notification rate in HIV-infected persons. Interaction between tuberculosis and HIV-infection predefines special considerations related to approach to organization of

antituberculosis activities for patients with immunodeficiency. Infection induced by human immunodeficiency virus that is not treated in the presented cases brings on immunodeficiency progression associated with tuberculosis development.

Presence of HIV-infection is the most significant risk factor for tuberculosis development. Probability of tuberculosis development in a person infected with HIV and with Mycobacterium tuberculosis is manifold higher than in a non-HIV-infected person. Risk of tuberculosis development in HIV-infected persons closely correlates to CD4+ lymphocyte count. The risk of latent, subclinical tuberculosis progression to the stage of full blown disease per annum is 5–15% in case of HIV-infection overlay. HIV destroys important cells of immune system, CD4 lymphocytes, thus, weakening organism's immunodefences. Immunity (including immunity for tuberculosis) affected by HIV gradually weakens. There is a high risk of tuberculosis development in a patient with HIV being in a direct close contact with an active TB patient. Tuberculosis that was not timely diagnosed and, therefore, untreated in a patient with HIV rapidly involves several organs and systems in the pathologic process contributing to unfavorable outcome.

HIV-infection notification rate has been exceeding tuberculosis notification rate since 2014 (exceedance by 11.1% in 2016), and HIV-infection prevalence rate began to exceed tuberculosis prevalence rate in 2008 (3.4-fold exceedance in 2016). There is accumulation of patient populations with HIV-infection, this is due to the fact that lethality rate among HIV-infected persons is rather low (3.7% in 2016) in comparison to patients being under regular medical check-up for tuberculosis (13.1% in 2016).

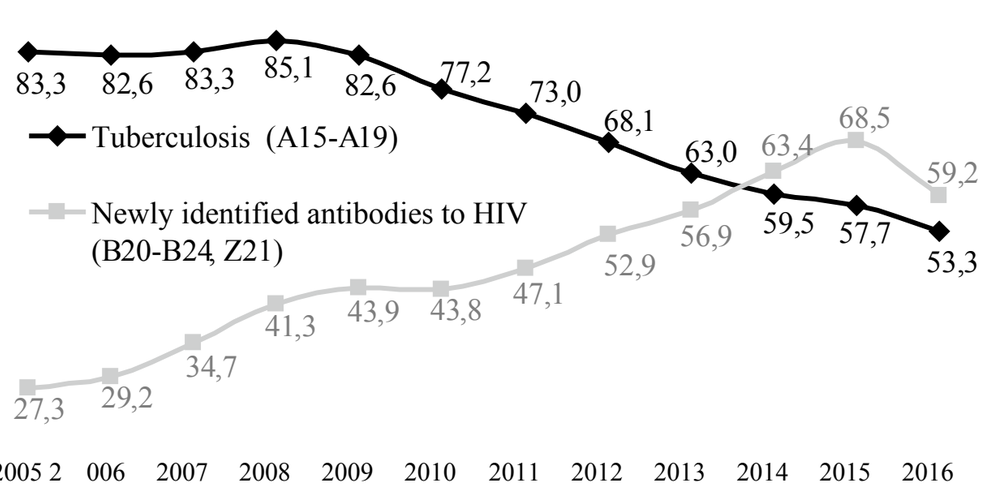

Figure 1.1. Notification rate of tuberculosis and HIV-infection in Russia (per 100 000 population).

In 2016, 658 141 HIV-infected persons were followed-up at AIDS centers, 20.9% of them were patients at late stages of disease. The proportion of patients at late stages of HIV-infection (those who predominantly develop tuberculosis) grows year on year: 2.8% in 2005; 11.3% in 2010; 15.9% in 2015; and 20.9% in 2016.

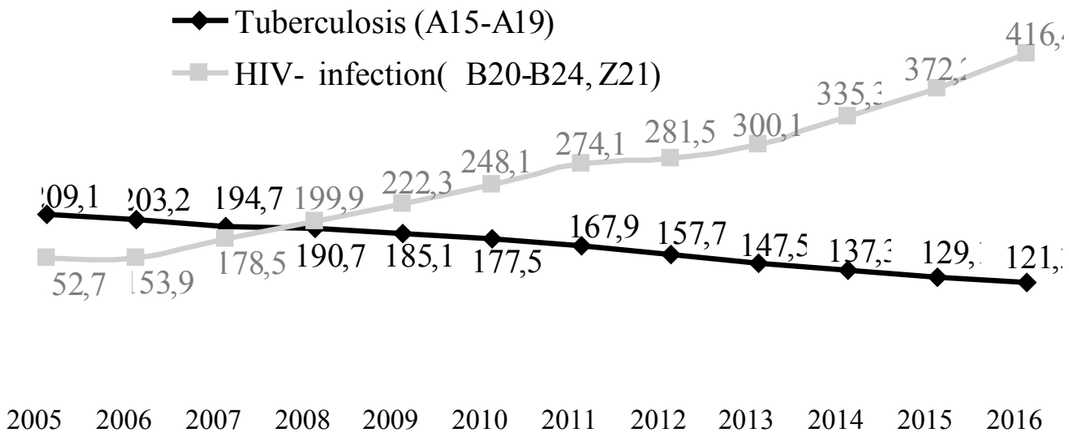

Figure 1.2. Prevalence rate of tuberculosis and HIV-infection at the end of the year among resident population of Russia (per 100 000 population).

In absolute numbers, in the intervening years, the number of patients at late stages has grown from 6 505 to 137 463 persons in 2016, i.e. by 21.1 times. The increasing tendency of the number of patients at late stages of HIV-infection is expected to continue. The process contributes to the growth of absolute number and proportion of patients with tuberculosis and HIV-infection combined (TB/HIV) among people who developed tuberculosis as well as to the unfavorable prognosis on TB epidemic situation after 2020.

The first single cases of tuberculosis in HIV-infected patients in Russia were registered in 1987. It has become possible to analyze the situation since 2009, when data on TB/HIV have been included in the forms of state statistical monitoring (Fig. 1.3-1.4).

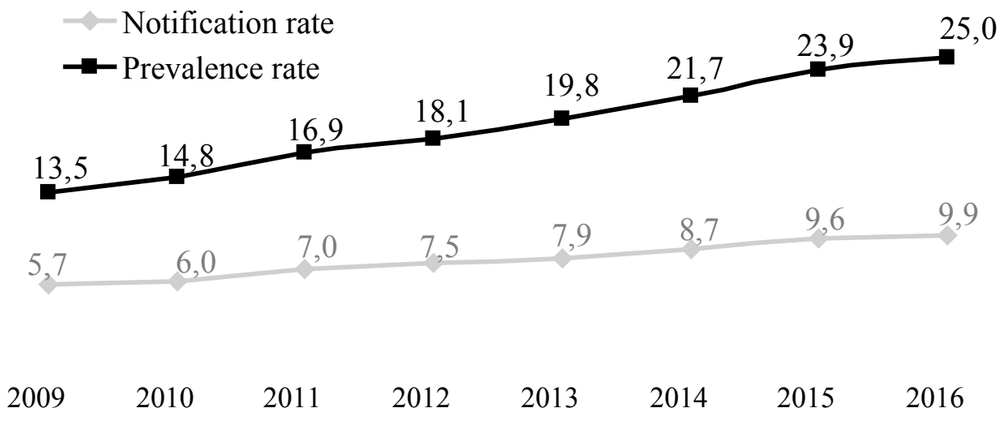

Figure 1.3. Notification rate and prevalence rate of TB/HIV at the end of the year in the Russian Federation, per 100 000 population.

Notification rate of tuberculosis and HIV-infection combined (among resident population and among people in penitentiary facilities of Russia) has grown by 73.7% from 2009 to 2016 (from 5.7 to 9.9 per 100 000 population), and prevalence rate at the end of the year grew by 85.2% (from 13.5 to 25.0 per 100 000 population).

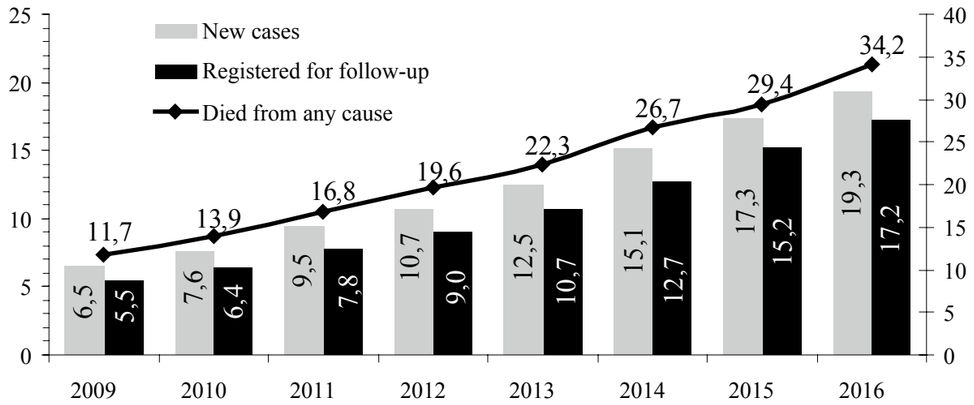

Figure 1.4. Proportion of HIV-infected persons in the structure of TB patients, being under follow up in Russia: newly registered for follow-up at the end of the year, died from any cause, %.

The proportion of patients with HIV-infection is increasing. Among new TB cases that were registered and followed-up in TB control facilities, it increased from 6.5% in 2009 to 19.3% in 2016, and among patients being under dispensary follow-up for tuberculosis at the end of the year, from 5.5% to 17.2%. Among TB patients who died from any cause, it increased from 11.7% to 34.2%.

Table 1.1 presents calculation of TB notification rate in patients with HIV-infection registered for follow-up and being permanent residents. Tuberculosis notification rates in HIV-infected patients were compared with tuberculosis rates excluding HIV-infected population. Tuberculosis notification rate in HIV-infected patients among permanent residents registered for follow-up in 2016 is 50.9 times higher (1 897.6 per 100 000 of HIV-infected persons) than on average for Russia without HIV-infected persons (37.3 per 100 000 population).

Differences in TB notification rate between HIV-infected persons and non-HIV-infected permanent residents of Russia are growing every year as the proportion of individuals at late stages of HIV-infection is increasing, and their TB notification rate is maximal and can come up to 15% per annum (Fig. 1.5).

TB notification rates in HIV-infected persons are largely influenced by overall epidemic situation for tuberculosis in the region, tuberculosis prevalence, and infection level of the population. A relatively low TB notification rate among HIV-infected persons is noted in the Central Federal Region (1 099.3 per 100 000 HIV-infected persons) and in the Northwestern Federal Region (1 085.1) of Russia, and

the highest rates are observed in the Siberian Federal Region (2 749.8) and in the Far-Eastern Federal Region (2 288.0). Similar situation is observed for tuberculosis notification rates in non-HIV-infected population, i.e., the most favorable situation is observed in the Central FR and Northwestern FR, and the hardest situation is noted in the Siberian FR and in the Far-Eastern FR.

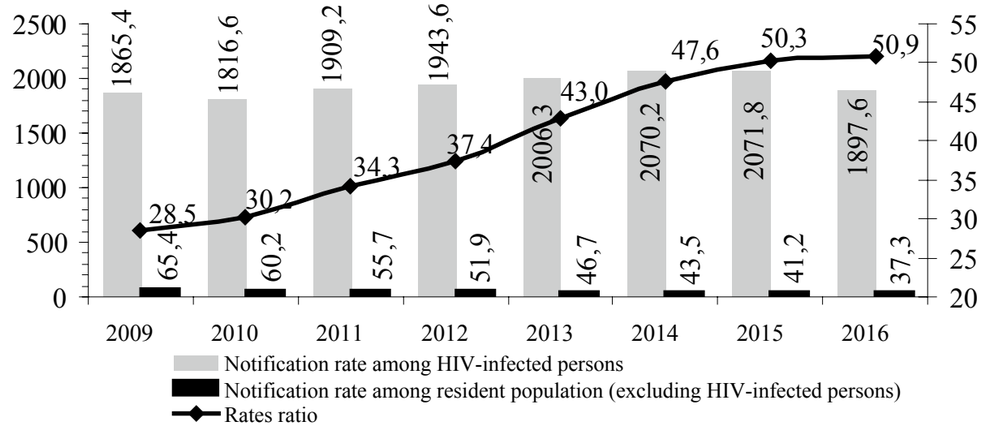

Figure 1.5. TB notification rate among resident population of the Russian Federation: HIV-infected persons and other population, per 100 000 population.

Table 1.1.

Tuberculosis notification rate among resident population of Russia in 2016 : HIV-infected persons and population without HIV-infection

Federal Regions of the Russian Federation	TB notification rate among resident population								
	Total		Incl.: TB/HIV			Incl.: tuberculosis without HIV-infection			
	abs. number	per 100 thous. population	abs. number	Ranking	per 100 thous. HIV	abs. number	Ranking	per 100 thous. without HIV	Notification: «TB /HIV» / «TB without HIV»
Total for Russia, incl.:	**66 891**	**45,6**	**12 489**		**1897,6**	**54 402**		**37,3**	**50,9**
Central FR	10 494	26,8	1 202	2	1099,3	9 292	1	23,8	46,2
Northwestern FR	4 255	30,7	711	1	1085,1	3 544	2	25,7	42,3
Southern FR	7 204	43,9	808	5	1920,7	6 396	5	39,1	49,1
North-Caucasian FR	3 151	32,3	108	3	1472,2	3 043	3	31,2	47,1
Povolzhsky FR	13 329	44,9	2 977	4	1859,3	10 352	4	35,1	53,0
Ural FR	7 524	61,0	2 376	6	2070,1	5 148	6	42,2	49,1
Siberian FR	15 854	82,0	3 987	8	2749,8	11 867	7	61,9	44,4
Far-Eastern FR	5 078	82,1	320	7	2288,0	4 758	8	77,1	29,7

Tuberculosis may occur in any phase of HIV-infection development, and its clinical manifestations clearly correspond to patient's immune status deficiency. If tuberculosis develops in HIV-infected persons at early stages of HIV-infection, the disease often manifests as the pulmonary TB. In the course of progression of immunosupression, tuberculosis of lymphatic system and lesion of serous membranes develop (tuberculosis of pleura, peritoneum and pericardium), and then tuberculous meningitis occurs. In case of extremely low CD4+ cells count, disseminated tuberculosis often develops.

HIV-infection may influence tuberculosis epidemiology in three different ways:

- endogenous reactivation of prior infection of M. tuberculosis in persons who get infected with HIV;
- progression of M. tuberculosis infection to active tuberculosis in persons, who are already HIV-infected;
- transmission of MbT from patients who developed tuberculosis due to HIV-infection to general population.

Maximum notification rates of tuberculosis and HIV-infection in Russia (Fig. 1.6-1.7) were at the age of 25-34 (women) and of 35-44 (men). The majority of patients get infected with tuberculosis, HIV-infection, and with tuberculosis associated with HIV-infection at a young productive (working) age (18-44).

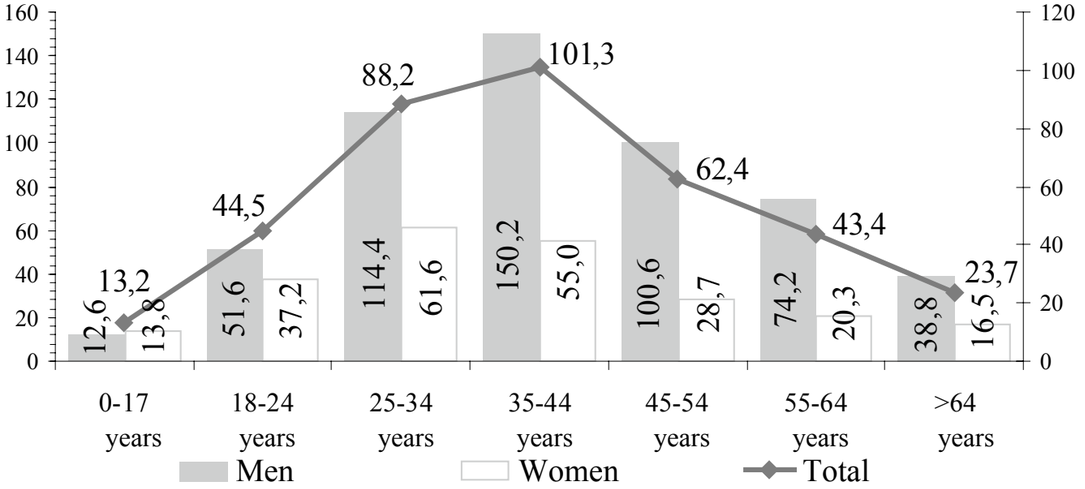

Figure 1.6. Tuberculosis notification rate in the Russian Federation in relation to gender and age in 2016 (per 100 000 population).

66.8% of patients developed tuberculosis at 0-44 years of age. Persons who developed tuberculosis (2016) were: 0-17 years of age, 4.9%; 18-24 years of age, 6.4%; 25-34 years of age, 27.8%; 35-44 years of age, 27.7%; 45-54 years of age, 15.6%; 55 years and older, 17.6%.

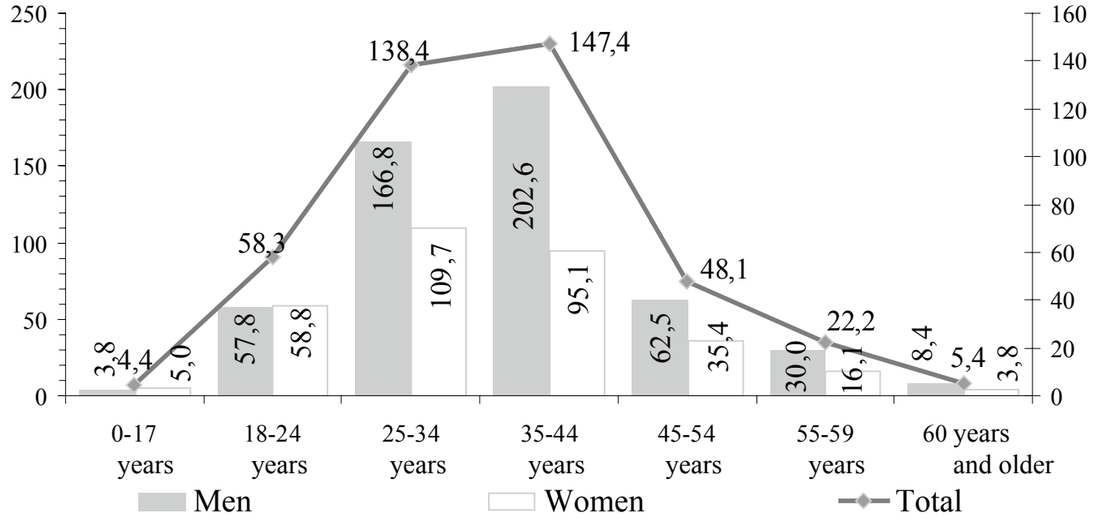

Figure 1.7. HIV-infection notification rate in the Russian Federation in relation to gender and age in 2016 (per 100 000 population).

In 84.5% of patients, first antibodies to HIV were indicated when patients were the age of 0-44. Persons who got infected with HIV(2016) aged: 0-17, 1.5%; 18-24, 7.5%; 25-34, 39.3%; 35-44, 36.2%; 45-54, 10.8%; 55 and older, 4.7%.

Mortality rate due to tuberculosis (Fig. 1.8) decreased by 65.5% (from 22.6 per 100 000 population in 2005 to 7.8 per 100 000 population in 2016) in Russia. Mortality rate due to HIV-infection has been exceeding TB mortality rate since 2015 (62.8% exceedance in 2016).

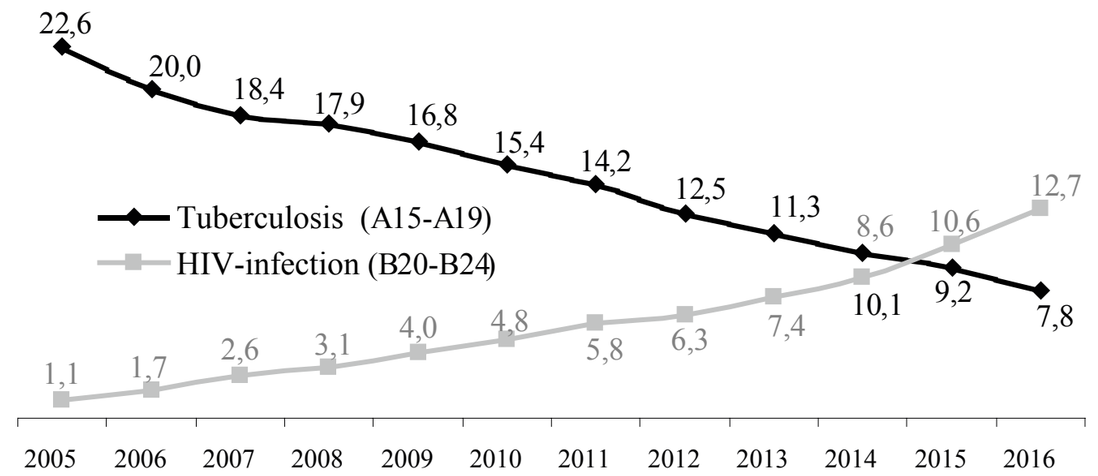

Figure 1.8. Mortality rate due to TB and HIV-infection in Russia (per 100 000 population).

Among persons who died of tuberculosis, the proportion of HIV-infected persons is decreasing, as «HIV-infection» diagnosis is put in the first place. As a result, the proportion of cases where tuberculosis is specified as a cause of death decreases in the structure of Russia's population mortality due to infectious and parasitic diseases (2005, 82.8%; 2015, 39.2%; 2016, 32.2%) with simultaneous increase of proportion of people who died of HIV-infection (2005, 3.9%; 2015, 45.2%; 2016, 52.6%).

HIV-infection at a young, productive (working) age (18-44) begins to occupy one of the leading positions in the population mortality structure. More people (8.6%) die of HIV-infection at the age of 18-44 (2016) than of malignant neoplasms (7.5%), respiratory diseases (4.0%), diseases of nervous system (2.0%), ischemic heart disease (5.2%), cerebrovascular diseases (3.0%), and tuberculosis (2.7%). Men die of HIV-infection more often (7.9%) than of malignant neoplasms (4.5%), ischemic heart disease (5.8%), cerebrovascular diseases (2.8%), respiratory diseases (4.0%), diseases of the nervous system (1.9%), and tuberculosis (2.7%). Women die of HIV-infection more often (10.8%) than of respiratory diseases (4.2%), ischemic heart disease (3.6%), cerebrovascular diseases (3.6%), diseases of the nervous system (2.5%), and tuberculosis (2.5%).

The peak of TB mortality rate (Fig. 1.9) falls at the age of 35-64 (71.8% of the number of deaths). Persons who died of tuberculosis (2015) aged: 0-24, 1.4%; 25-34, 15.7%; 35-44, 26.4%; 45-54, 24.3%; 55-64, 21.1%; 65 and older, 10.2%.

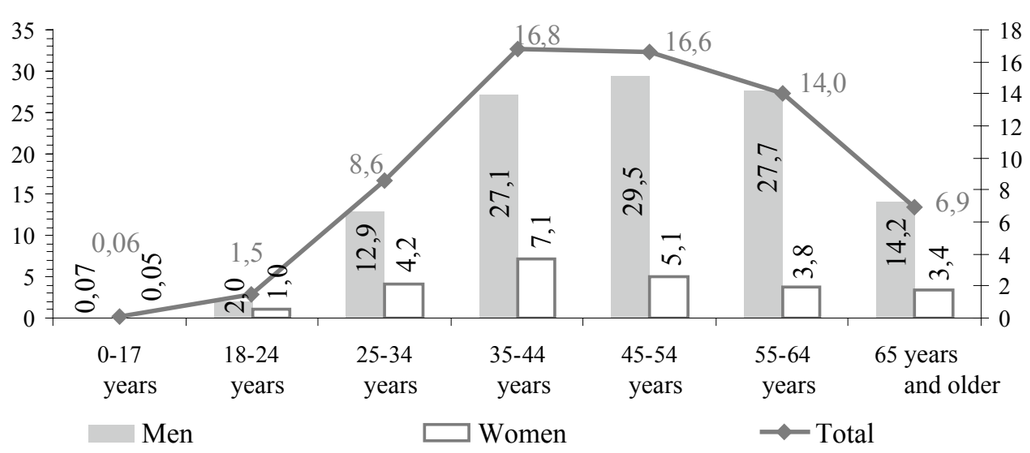

Figure 1.9. Mortality rate due to tuberculosis in the Russian Federation in relation to gender and age in 2015 (per 100 000 population).

The peak of HIV-infection mortality rate (Fig. 1.10) falls at the age of 25-44 (83.1% of the number of deaths). Persons who died of HIV-infection (2015) aged: 0-24, 2.0%; 25-34, 38.1%; 35-44, 45.0%; 45-54, 10.9%; 55 to 64, 3.1%; 65 and older, 0.6%.

Persons who died of HIV-infection (2016) aged: 0-24, 1.6%; 25-34, 33.6%; 35-44, 48.0%; 45-54, 12.3%; 55-64, 3.5%; 65 years old and >, 0.7%. That means that deaths began to occur at an older age.

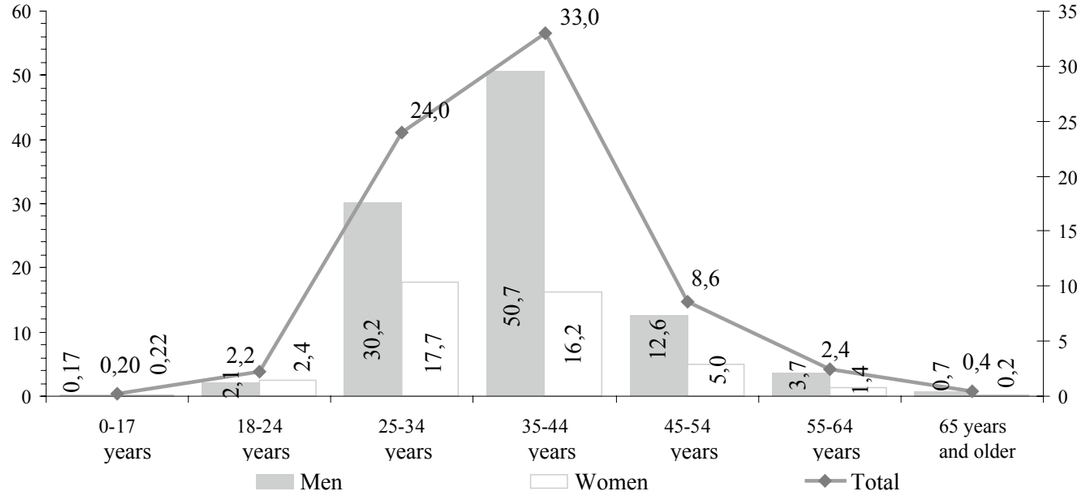

Figure 1.10. Mortality rate due to HIV-infection in the Russian Federation by gender and age in 2015 (per 100 000 population).

While the peaks of tuberculosis and HIV-infection notification rates fell at similar age groups of young age both in men and in women, the same cannot be said of mortality rates of these socially significant infectious diseases. Patients die of HIV-infection predominantly at the young age of 25-44 (more than 80%). Patients in the age group of 25-44 die even more often than during HIV-infection first registration (75.5%) on the account of deaths that occurred in patients who got infected under the age of 25.

Patients in the age group of 25-44 die of tuberculosis much more rarely (40%) than of HIV-infection. Moreover, the majority of new TB patients (55.5%) was in the age group of 25-44. Older age of persons who died of tuberculosis is to a large extent related to peculiarities of registration of causes of death. Young patients who have actually died of tuberculosis are registered as deaths due to HIV-infection. Every second patient registered as one who died of HIV-infection actually died of tuberculosis progression at late stages of HIV-infection. Assessment of the number of deaths caused by tuberculosis in patients with HIV-infection is presented as death caused by HIV-infection (code ICD-10 – part B20.0, B20.7, B22.7).

Permanent residents followed-up for tuberculosis in 2016 who were infected with HIV and died from any cause were registered as patients who died of tuberculosis only in 3.7% of cases (302 of 8 217 HIV-infected tuberculosis patients who died from different causes).

Among patients who were under dispensary follow-up for tuberculosis and died of tuberculosis, the number of HIV-infected patients decreased: 1 148 patients in 2009, 643 patients in 2015, and 302 patients in 2016. Simultaneously, the number of TB patients who were infected with HIV and died from other reasons increased: 2 562 patients in 2009, 6 768 patients in 2015, and 7 915 patients in 2016. In lethality structure of TB patients, the proportion of patients who died of tuberculosis decreased: 56.3% in 2009; 39.1% in 2015; 34.8% in 2016.

In 2016, in 45 subjects of Russia, all cases of death were registered as «HIV-infection» when a tuberculosis patient died of tuberculosis but was HIV-infected, even if immunity decrease was not observed for the cause of death to be registered as HIV-infection.

In industrially developed countries, tuberculosis epidemic development in the long run is likely to be influenced by multiple factors, including migration of population from countries with high tuberculosis prevalence rate. It is expected that in the majority of countries of Western Europe HIV-infection will only small part as segments of population at the highest risk of HIV-infection ingression are rapidly substituted by persons practically non-infected with tuberculosis. Despite the fact that HIV-infection may bring on growth of number TB cases among HIV-infected drug addicts, it is unlikely that this growth may significantly influence the overall notification rate in the native population of these countries.

The situation in countries with low level of income is different. Tuberculosis and HIV-infection are two closely related conditions, as prevention of the first disease depends on condition of cell immunity, and the second one destroys this particular part of the immune system. Thus, it may be expected that tuberculosis situation may worsen in many countries with low level of income in the nearest future.

Tuberculosis epidemic process development in Russia will be significantly influenced by peculiarities of organization and level of execution of TB control activities among HIV-infected persons: promptness of TB screenings, quality of tuberculosis chemoprevention at late stages of HIV-infection, vaccination of children born to HIV-infected mothers with BCG vaccine, timeliness and quality of antiretroviral and antituberculous treatment of new TB patients.

Chapter II

Tuberculosis associated with HIV-infection in Penitentiary facilities of the Russian Federation

T.Y. Chebagina, Y.A. Samarina, S.A. Sterlikov

Persons held in penitentiary facilities belong to population category that is vulnerable both to tuberculosis and to HIV-infection. They are quite reasonably expected to have high rate of combined TB/HIV infection.

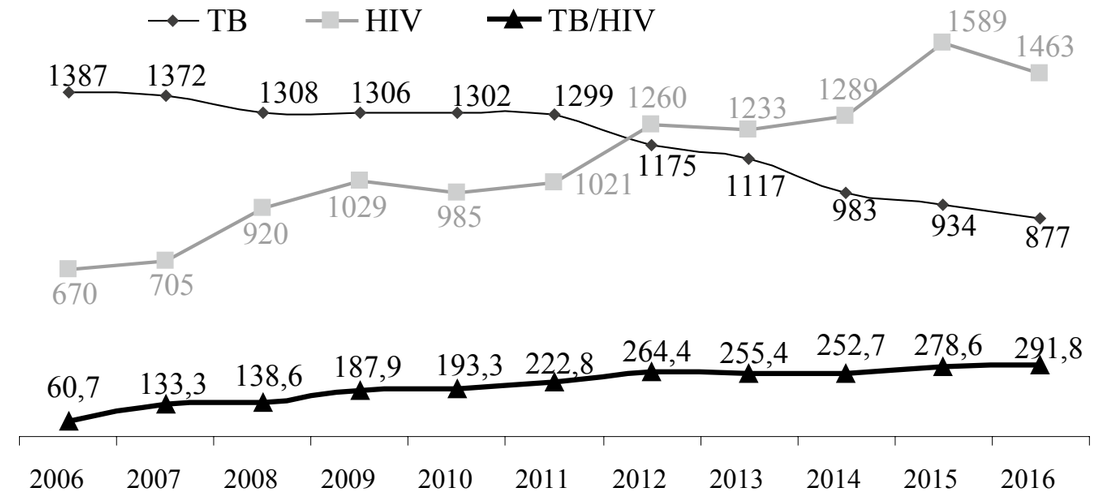

Figure 2.1. The dynamics of notification rate of tuberculosis (TB), HIV-infection (HIV) and TB/HIV among suspects, accused, and convicted persons in penitentiary facilities of Russian Federation.

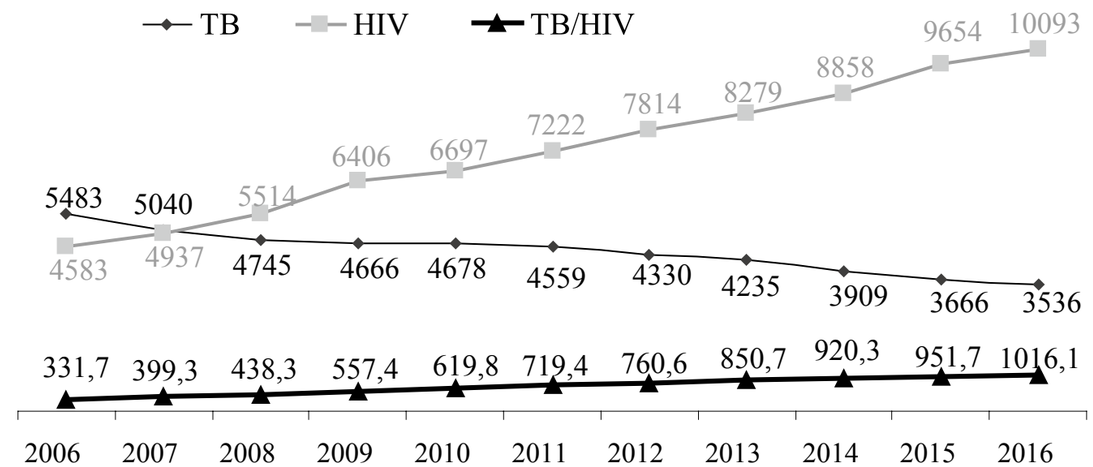

Figure 2.2. The dynamics prevalence rate of tuberculosis (TB), HIV-infection (HIV), and TB/HIV among suspects, accused, and convicted persons in penitentiary facilities of Russian Fedrration.

Nowadays, in contrast to 1.5-fold decrease of TB notification rate among suspects, accused, and convicted persons, a two-fold growth of HIV-infection notification rate is noted in this group as well as almost five-fold (by 4.8 times) increase in TB/HIV co-infection (Fig. 2.1). Similar situation is noted regarding prevalence rate of these diseases (Fig. 2.2). Along with a 1.5-fold (1.6 times) decrease of active tuberculosis prevalence rate, a two-fold (2.2 times) growth of HIV-infection prevalence rate and a three-fold (3.1 times) increase of TB/HIV co-infection prevalence rate is noted.

Under current conditions, it appears reasonable to analyze the source of TB/HIV notification rate at the place of detection: new TB/HIV cases detected at pretrial detention centers ("SIZO") are mostly cases detected during primary screening carried out after incarceration to detention facilities, i.e. they are persons who developed the disease in conditions of public healthcare. New cases detected at correctional facilities are persons who actually developed the disease in penitentiary facilities. The dynamics of TB/HIV notification rates in pretrial detention centers and correctional facilities is shown in the graph (Fig. 2.3).

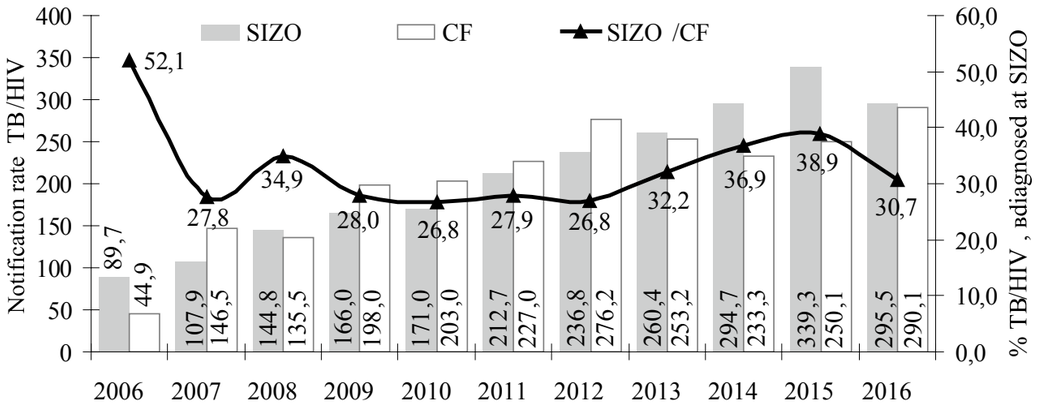

Figure 2.3. The dynamics of TB/HIV notification rates in pretrial detention centers (SIZO) and correctional facilities (CF) as well as proportion of new TB/HIV patients detected in SIZO (in % of all new TB/HIV cases).

TB/HIV notification rates in pretrial detention centers and correctional facilities increased nearly synchronously. This backs up the thesis introduced by O.B. Nechayeva in previous chapter on significant impact of HIV-infection stages on TB/HIV notification rate; what is more, even in conditions of significant decrease of TB notification rate, the growth of combined pathology notification rate does not stop but continues its progression. Furthermore, TB/HIV progression takes place in conditions of implementation of standard activities complex, i.e. coverage of HIV-infected suspects, accused and convicted persons with antiretroviral therapy, preventive therapy of latent TB infection and other activities aimed at immunosuppresion prevention and tuberculosis prophylaxis. In view of this, further escalation of TB/HIV problem may be anticipated not only in public healthcare system, but also in penitentiary facilities.

Geographical peculiarities of TB/HIV notification distribution are shown in Fig. 2.4.

Figure 2.4. Geographical peculiarities of TB/HIV notification in penitentiary facilities of the Russian Federation in 2016. The darker coloring corresponds to a higher rate of TB/HIV notification.

TB/HIV notification rate generally corresponds to drug traffic from Afghanistan, though it additionally affects neighboring regions with high tuberculosis notification rate. Correlation analysis regarding notification rate of TB/HIV, tuberculosis and HIV-infection reveals average correlation between TB/HIV notification rate and tuberculosis notification rate (s=0.6), and between TB/HIV notification rate and HIV-infection notification rate (s=0.5). Correlation dependence between tuberculosis notification rate and HIV-infection notification rate is weak (s=0.3). It proves that TB/HIV notification rate is in almost equal measure maintained by tuberculosis and HIV-infection; at the same time, the impact of HIV-infection is still not sufficient enough at the time to significantly maintain tuberculosis notification rate among socially deprived segments of population.

Data of statistics make it possible to evaluate the dynamics of HIV-infection notification rate and prevalence rate in correctional facilities (without pretrial detention centers) with regard to gender composition of convicted persons (table 2.1).

Table 2.1.

The dynamics of the epidemic situation for TB/HIV in correctional facilities of the Russian Federation with regard to gender of convicted persons.

Years	TB/HIV prevalence rate		% of TB/HIV among TB-patients		TB/HIV notification rate	
	Men	Women	Men	Women	Men	Women
2006	313,6	152,4	5,2	7,2	85,7	45,9
2007	433,3	208,5	7,6	12,7	136,2	87,7
2008	425,2	287,2	7,9	15,8	129,7	90,2
2009	591,0	323,4	11,3	17,7	185,3	136,8
2010	630,5	368,7	12,1	20,7	197,1	94,9
2011	739,3	501,1	14,6	24,8	205,2	219,9
2012	774,4	666,9	16,1	30,4	224,5	247,4
2013	836,4	638,7	21,7	31,5	238,6	242,2
2014	895,0	617,6	20,6	28,7	216,1	237,5
2015	930,2	804,1	22,7	39,3	217,6	163,2
2016	1045,3	1015,1	26,2	49,3	234,5	140,5

In the period from 2006 to 2016, TB/HIV prevalence rate increased by 6.7 times in women held in correctional facilities and by 3.3 times in men; the proportion of TB/HIV patients among all TB patients held in correctional facilities also increased more rapidly in women than in men, i.e. by 6.8 and 5.0 times, respectively. The ratio of combined TB/HIV pathology prevalence rate among men and women changed significantly: in the period from 2006 to 2007 it was 2.1, and in 2016 it became equal (1.0).

Proportion of TB/HIV patients among all TB patients in correctional facilities increases both among men and women; however, the proportion of women with TB/HIV exceeds the proportion of men with TB/HIV by 1.7+0.2 times on the average.

Gender peculiarities of the dynamics of combined pathology prevalence rate and the proportion of patients with TB/HIV in men and in women in correctional facilities are related both to gender peculiarities of tuberculosis notification [8] and to gender peculiarities of HIV-infection notification: women are more often convicted of non-violent crimes connected with distribution of drugs [19]. Tuberculosis prevalence rate decreased by 1.5 times in men in correctional facilities from 2006 to 2016, from 6020.7 to 3995.3 while tuberculosis prevalence rate in women only decreased from 2104.6 to 2059.3; the ratio between female and male TB patients held in correctional facilities decreased from 2.9 to 1.9. Theoretical rate of positive immunoblotting test results increased from 6864.9 to 11419.9 (by 1.7 times) in men, and from 16357.8 to 24836.2 (by 1.5 times) in women in correctional facilities in the period from 2007 to 2015. The ratio of theoretical rate of positive immunoblotting test results in women to theoretical rate of positive immunoblotting test results in men was 2.2 (2015) to 2.8 (2011) throughout the period of observation. Thus, HIV-infection problem in women is much more pronounced than in men in correctional facilities of the Russian Federation. This may be due to increasing involvement of women in illicit psychoactive drug trafficking [6] including injectible drugs.

Notification rate of TB/HIV in men and women held in correctional facilities is variable. That may be related to concurrent influence of tuberculosis infection and HIV-infection. Nevertheless, there is a rather consistent increasing tendency noted in men but absent in women. Reasons for high variability of the specified indicator in women require further investigation.

Thus, despite TB notification rate decrease, a significant growth of notification and prevalence rate of TB/HIV exceeding HIV-infection growth is noted in penitentiary system of Russian Federation. It may be related to increasing number of cases in late stages of HIV-infection. High notification rate of TB/HIV is geographically connected to drug traffic from Afghanistan. TB/HIV prevalence rate grows more rapidly in women than in men in correctional facilities. It resulted in change of TB/HIV patients gender ratio, women held in correctional facilities at present moment have TB/HIV as often as men. Among tuberculosis patients, the proportion of women with TB/HIV is by 1.7 times higher than the proportion TB/HIV of men. A search for preventive measures for TB/HIV is required primarily for women held in penitentiary facilities.

Note. Overall notification rate in penitentiary facilities was calculated as ratio of the number of new patients (multiplied by 100 000) to sum of the average number of convicted persons in correctional facilities and the number of individuals newly detained at pretrial detention centers. Overall prevalence rate in penitentiary facilities was calculated as ratio of the number of patients inmate at the end of the reporting year (multiplied by 100 000) to the average number of suspects, accused and convicted persons. Notification rate at pretrial detention centers was calculated as ratio of the number of new patients diagnosed at pretrial detention centers (multiplied by 100 000) to the number of individuals newly detained. Notification rate in correctional facilities was calculated as the number of new patients diagnosed at correctional facilities (multiplied by 100 000) to the average number of convicted persons held at correctional facilities. Correlation coefficient between tuberculosis, HIV-infection, and TB/HIV notification rates in subjects of the Russian Federation was calculated as per Spearman method (s).

Chapter III

Presentation of the issue of tuberculosis and HIV-infection in WHO Global Report. Principles of the research on detection, diagnosis and treatment of patients with tuberculosis associated with HIV-infection

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WHO annually forms a Global Tuberculosis Report. Compilation of the report is carried out on the basis of data submitted by WHO member states (including the Russian Federation) in standard WHO Global Report forms.

WHO publishes the following information in the Global Tuberculosis Report:

- TB/HIV epidemic situation;
- tuberculosis patients testing for HIV-infection and activities on screening people living with HIV for tuberculosis;
- coverage of patients TB/HIV of antiretroviral therapy;
- treatment outcomes for patients with TB/HIV (new cases, relapses and patients with rifampicin-resistant tuberculosis);
- tuberculosis preventive therapy in people living with HIV;
- financing of activities aimed at TB/HIV control;
- effectiveness of activities aimed at TB/HIV control (number of prevented deaths).

For this purpose, WHO collects a wide array of information from member states, which serves for compiling the specified data. Most of the information is absent in standard forms statistic. Data that make it possible to receive an overview of financing of TB/HIV infection control has been collected since 2012.

In the course of preparation of the information for the First Global Ministerial Conference on Tuberculosis in the context of Global Healthcare Development and Millennium Goals, a task was set to publish additional statistical data in the WHO Global Tuberculosis Report that had not been collected before due to collection process being extremely labor-consuming, and also results of TB/HIV patients' treatment.

The latter task was fulfilled in an unofficial way by voluntary participation of subjects of the Russian Federation that maintain electronic register of tuberculosis patients allowing to perform upload in a particular format.

In general, 9 subjects of the Russian Federation submitted results of treatment of TB/HIV patients and tuberculosis patients without HIV-infection: Irkutsk, Kostroma, Novgorod, Lipetsk, Tula, and Tyumen Oblasts, and Republics of Karelia, Crimea, Tatarstan, and Sevastopol city. Additionally, results of treatment for TB/

HIV patients only were submitted by Penza and Smolensk Oblasts, Kamchatka Krai, and Chuvash Republic. The latter data were included in the WHO Global Tuberculosis Report but were not included in the further study as there was no control group to compare data obtained for TB/HIV patients with similar data for tuberculosis patients without HIV. Nevertheless, their data were included in the WHO Global Tuberculosis Report which made it possible to increase the number of TB/HIV treatment cases in the Global Report.

Treatment outcomes of TB/HIV patients included in the WHO Global Tuberculosis Report are presented in Fig. 3.1.

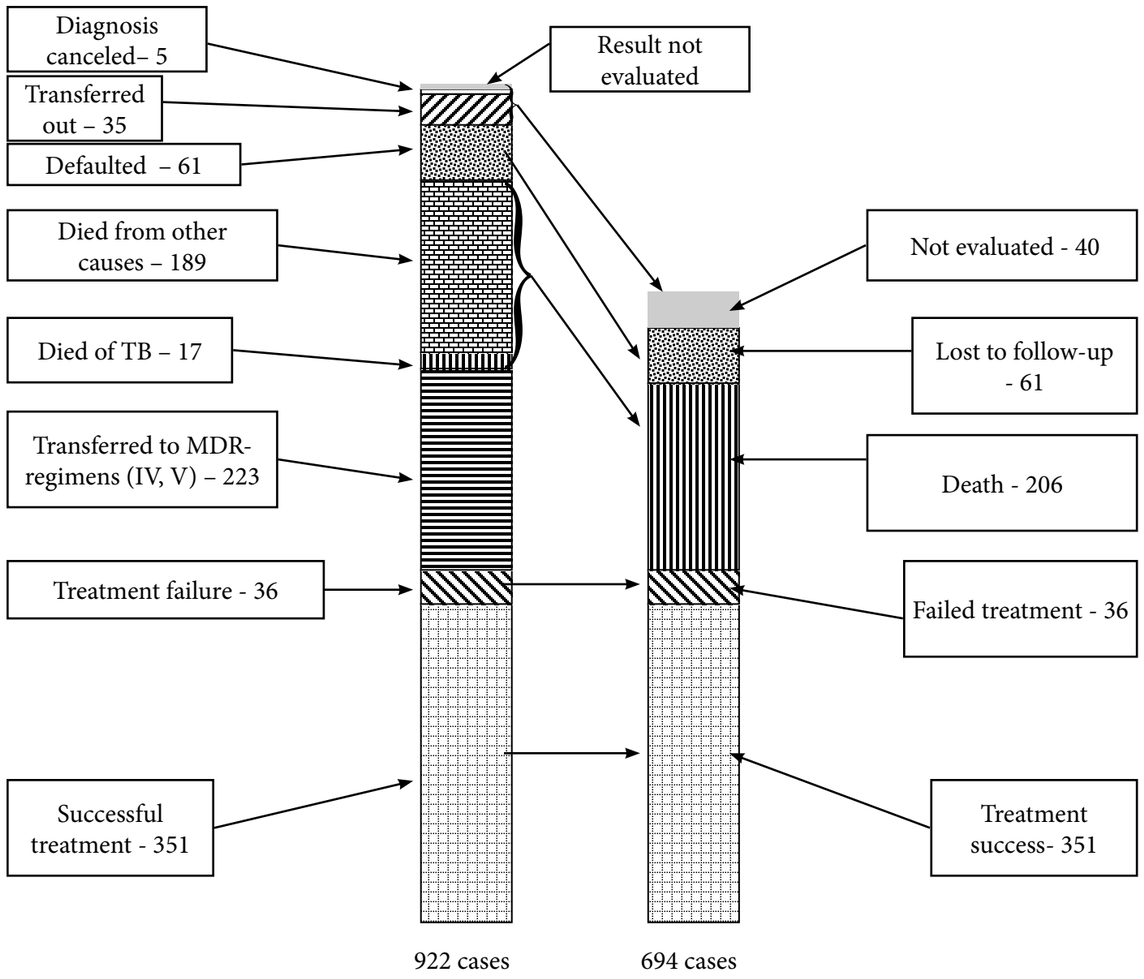

Figure 3.1. Compilation of data for the WHO Global Report on TB/HIV cases treatment results in the Russian Federation based on the material obtained during the study.

Patients registered for treatment as per MDR-regimens were excluded from the data submitted for the WHO Global Report in accordance with the rules

of data submission. Similarly, patients whose tuberculosis diagnosis had been canceled were excluded. Patients who died of tuberculosis and from other causes were presented as overall number of those who died from all causes; as the mortality rate due to tuberculosis and not due to tuberculosis is not differentiated in the WHO Global Report. Outcome "Defaulted" completely corresponded to WHO outcome "Lost to follow-up". Such outcomes as Transferred out and cases not evaluated for any reason (including patients who continue treatment) were submitted to the Global Report in accordance with WHO definitions as cases for which outcome of chemotherapy treatment course was not evaluated.

The comparison of TB/HIV cases treatment outcomes (new cases and relapses) in the Russian Federation (for patients registered for treatment in 2015) with outcomes of similar patients across all WHO regions and in the WHO European region (for patients registered in 2014) is presented in figure 3.2.

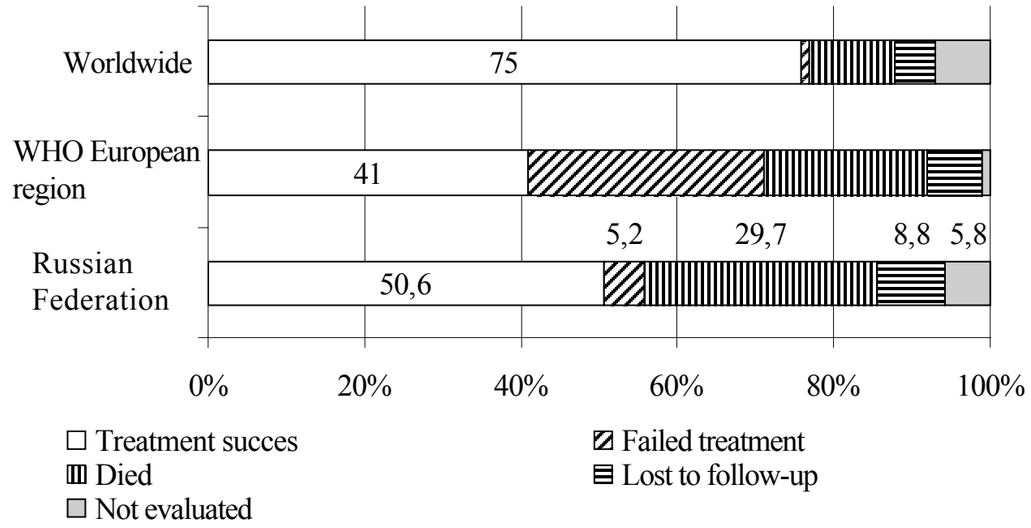

Figure 3.2. Treatment outcomes in TB/HIV patients worldwide, in the WHO European region, and in the Russian Federation.

As for proportion of patients with treatment success, the Russian Federation falls in between the worldwide and the WHO European region rates. The rate of failed treatment in the Russian Federation is minimal and comes up to the worldwide rate. Nevertheless, a high proportion of patient deaths is reported in the Russian Federation. The proportion of patients who were lost to follow-up in the Russian Federation is also higher than in the WHO European region and worldwide, though that is not that significant. The Russian Federation also occupies intermediate position for the number of treatment outcomes that

were not evaluated; the proportion of such outcomes in Russian Federation is less than worldwide, though it is several times higher than in the WHO European region.

The revealed tendencies confirm the necessity of conducting a focused research to assess reasons of insufficient effectiveness of TB/HIV patients treatment in the Russian Federation. The research was initiated by the Federal Center of Monitoring of Tuberculosis Control in the Russian Federation, and it was conducted by virtue of extensive cooperation.

Eligibility criterion was a possibility to form a specifically formatted depersonalized electronic table containing data in a certain format both for patients with TB/HIV and for tuberculosis patients without HIV-infection.

In total, data on 834 TB/HIV cases (680 new patients and 154 patients with relapse tuberculosis) and 6170 tuberculosis cases without HIV-infection (5238 new patients and 932 patients with relapse tuberculosis) were included in the research.

The sample size obtained was representative enough to estimate the characteristics of the overall general population with no less accuracy than 95% (and in the majority of cases, 99%) and with error of 5%. Results of the research are applicable for use in both clinical practice and making administrative decisions.

The research character permitted missing data. For this reason, groups of TB/HIV patients and tuberculosis patients without HIV-infection were formed taking into consideration missing data for each study; i.e. the number of patients in the specified groups varied in different studies.

Chapter IV

Age and gender peculiarities and clinical characteristics of patients with tuberculosis associated with HIV-infection

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As long as TB/HIV co-infection occurrence is associated with introduction of HIV-infection, it would be reasonable to expect that there are age peculiarities of TB/HIV development. In order to identify age peculiarities of TB/HIV (TB/HIV+) co-infection development, we compared the age of new tuberculosis patients with TB/HIV+ to the age of similar patients without HIV-infection (TB/HIV-). The result of the comparison is presented in Fig. 4.1, and in more detail in table 4.1.

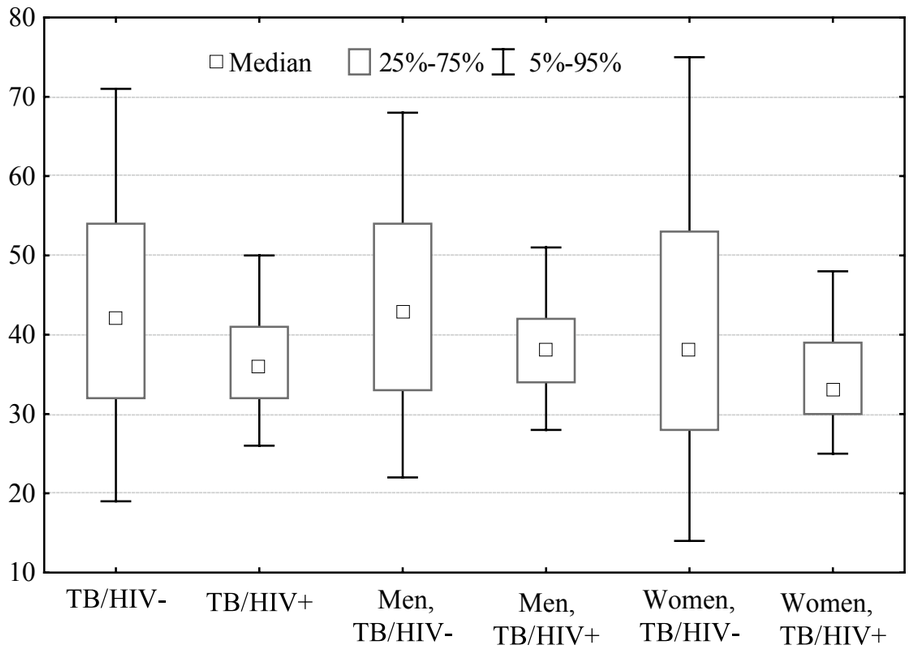

Figure 4.1. New cases of TB/HIV+ and TB/HIV- age distribution.

Table 4.1.

Detailed data on age quartile analysis of new TB patients with TB/HIV+ and TB/HIV-

Group of new TB panients	abs. number	Quartiles					Interquartile interval
			25%	Median	75%	97,5%	
TB/HIV-	5935	13	32	42	54	76	15,9
TB/HIV+	815	24	32	36	41	54	7,9
Men, TB/HIV-	4094	17	33	43	54	74	14,8
Men, TB/HIV+	573	26	34	38	42	54	7,7
Women, TB/HIV-	1840	6	28	38	53	78	17,9
Women, TB/HIV+	242	23	30	33	39	54	7,7

In general, new tuberculosis patients with TB/HIV co-infection are younger than similar patients without HIV-infection. Moreover, age range of co-infection development was narrower than that for tuberculosis patients without HIV-infection. In TB/HIV patients, more than a half of all values fell within the limits of 8 to 9 years: 34 to 42 years for men, and 30 to 39 years for women. What is more, 97% of patients with co-infection were of productive (working) age group, while the proportion of TB patients without HIV-infection at productive (working) age was 80%.

Both in case of tuberculosis without HIV-infection and in case of HIV-associated tuberculosis, women were younger than men approximately by 5 years.

The proportion of children under 18 years of age among new tuberculosis patients with co-infection was 0.9%, while it was 1.7% among tuberculosis patients without HIV-infection.

The proportion of persons over productive (working) age among new TB cases with co-infection was 2.1%, while it was 16.7% among all new TB cases.

It would be reasonable to expect that there are not only age but also gender peculiarities of new tuberculosis patients with TB/HIV+ and with TB/HIV-, yet there is none. Male to female (M/F) ratio among TB/HIV- patients was 2.2, and among HIV+ patients it was 2.4. Odds ratio was 1.06, $p>0.1$ (differences of low statistical significance). Thus, there are no significant gender differences between new tuberculosis patients with HIV-infection and without it.

The number of relapse tuberculosis patients was substantially smaller; nevertheless, analysis of age-gender structure of this group of patients was also carried out (Fig. 4.2).

Больных рецидивом туберкулёза было существенно меньше, тем не менее, для них также был проведён анализ возрастно-половой структуры (рис. 4.2).

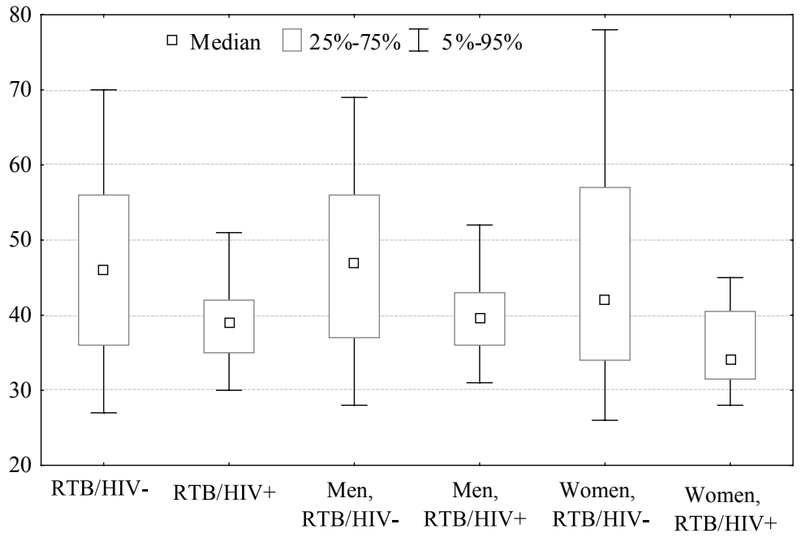

Figure 4.2. Age structure of relapse tuberculosis cases with co-infection (RTB TB/HIV+) and without it (RTB TB/HIV-).

Table 4.2.

Detailed data on age quartile analysis of patients with relapse tuberculosis, RTB/HIV+ and RTB/HIV-

Group of patients	abs. number	Quartiles					Interquartile interval
		2,5%	25%	Median	75%	97,5%	
RTB/HIV-	905	25	36	46	56	76	20
RTB/HIV+	152	28	35	39	42	53	7
Men, RTB/HIV-	722	25	37	47	56	74	19
Men, RTB/HIV+	120	30	36	39	43	53	7
Women, RTB/HIV-	183	23	34	42	57	82	23
Women, RTB/HIV+	32	27	31	34	40	47	9

In common with new tuberculosis cases, relapse tuberculosis cases with co-infection are characterized by a younger age within narrower limits of the age group.

The proportion of relapse tuberculosis in persons over productive (working) age without co-infection was 18.9%; and in relapse tuberculosis patients with co-infection, relapses were observed only in persons of productive (working) age.

M/F ratio was 3.8 (in RTB/HIV-) and 3.9 (in RTB/HIV+), i.e. gender profile of relapse tuberculosis patients with HIV infection and without it was similar.

Along with age and gender, patient's place of residence is an important characteristics to be analyzed. It is related to the fact that tuberculosis and HIV-infection prevalence

rates among urban and rural residents may differ significantly. Among new tuberculosis patients with HIV co-infection, the ratio of urban residents to rural residents was 3.8, while among new tuberculosis patients without HIV-infection, it was 2.1 (OR=1.8; p<0.01). In patients with relapse tuberculosis with TB/HIV co-infection, the ratio of urban residents to rural residents was 4.5, while in similar patients without co-infection it was 1.9 (OR=2.4; p<0.01). Thus, living in town may be considered an additional risk factor of TB/HIV co-infection.

The majority of studies [1, 12, 15, 17, 18], including the systematic review [9], showed that extrapulmonary tuberculosis (all forms of tuberculosis except pulmonary tuberculosis, by WHO definition) occurs more often in patients with TB/HIV+ than in patients with TB/HIV-. Moreover, MbT excretion confirmed by smear microscopy and destruction of pulmonary tissue are more rarely detected in this group [12, 17, 18]. Our research showed that extrapulmonary tuberculosis occurs 1.8 times more often in TB/HIV+ patients than in tuberculosis patients without HIV. Furthermore, the ratio was 2.1 for men, and only 1.4 for women. Registry data make it possible to subdivide extrapulmonary forms of tuberculosis into tuberculosis of pleura, intrathoracic lymph nodes, upper respiratory tract (respiratory extrapulmonary tuberculosis, REPTB), and extrarespiratory tuberculosis (ERTB). REPTB was observed in TB/HIV+ patients 1.8 times more often than in tuberculosis patients without HIV. It was typical both of men (2.0 times; p<0.01) and women (1.7 times; p<0.01). As for ERTB, it was noted in TB/HIV+ patients 1.8 times more often than in tuberculosis patients without HIV. Moreover, ERTB was observed in men 2.3 times more often than in women (p<0.01); and ERTB was observed in women with TB/HIV+ almost as often as in female tuberculosis patients without HIV (p>0.1).

Destruction of pulmonary tissue and MbT excretion are important clinical characteristics of tuberculosis. The presence of Destruction of pulmonary tissue was studied in 575 patients with pulmonary tuberculosis associated with HIV-infection (PTB/HIV+) including 397 men and 178 women. Control group consisted of 4757 patients with pulmonary tuberculosis without HIV-infection (TB/HIV-) including 3227 men and 1530 women. The rate of destruction of pulmonary tissue occurrence in these patients is shown in Fig. 4.3.

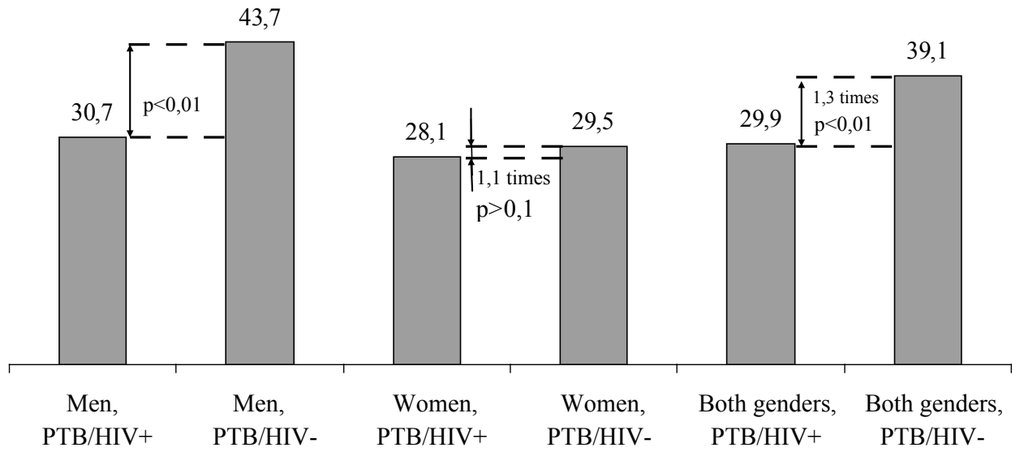

Figure 4.3. The rate of destruction of pulmonary tissue occurrence in new patients with pulmonary TB with HIV-infection (PTB/HIV+) and without it (PTB/HIV-).

Destruction of pulmonary tissue occurred 1.3 times more rarely in new patients with pulmonary tuberculosis associated with HIV-infection (PTB/HIV+) than in similar patients without HIV-infection (PTB/HIV-), 29.9% and 39.1%, respectively. This ratio was characteristic of men (destruction of pulmonary tissue were observed in PTB/HIV+ men 1.4 times more rarely than in PTB/HIV- men, 30.7% and 43.7%, respectively), though it was not characteristic of women (1.1 times, 28.1 and 29.5, respectively; p>0.1).

The smaller rate of destruction of pulmonary tissue in TB/HIV+ patients in comparison with TB/HIV- patients may be due to the mechanism of tuberculosis hematogenic spreading which results in disseminated tuberculosis.

The proportion of new patients with MbT excretion confirmed by smear microscopy was studied for 573 PTB/HIV+ patients (including 394 men and 179 women) and 4705 PTB/HIV- patients (including 3202 men and 1503 women) – Fig. 4.4.

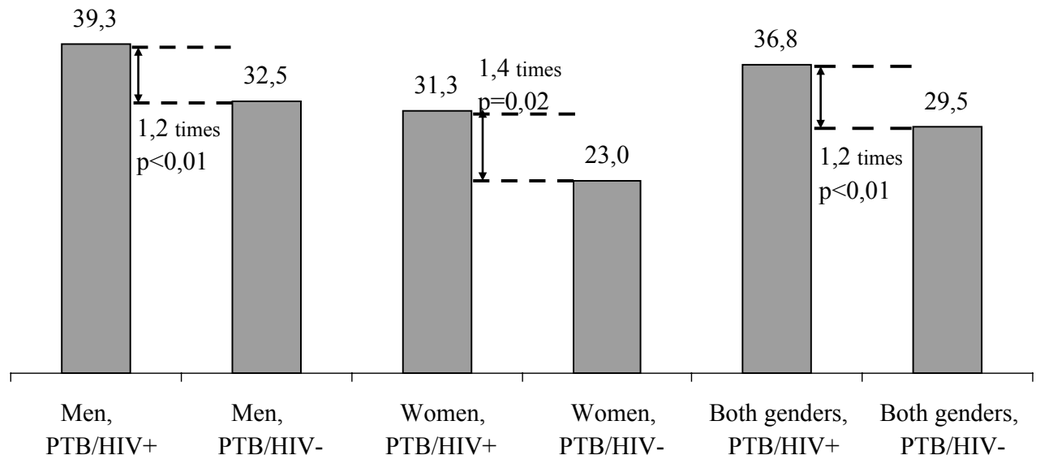

Figure 4.4. Frequency of MbT excretion, confirmed by smear microscopy in new pulmonary tuberculosis patients with HIV-infection (PTB/HIV+) and without it (PTB/HIV-).

Out of accord with results of a number of studies, MbT excretion was reported in PTB/HIV+ patients even more often than in PTB/HIV- patients. Most likely, it is a case of inhomogeneity of sample upon the criterion of active tuberculosis detection.

Nevertheless, we compared the intensity of MbT excretion in TB/HIV+ and PTB/HIV- patients, and differentiated relatively low MbT excretion (1 to 9 AFB per 100 fields of view) and extremely intensive MbT excretion (3+, i.e. more than 10 AFB per 1 field of view).

Relatively low MbT excretion was characteristic of PTB/HIV+ patients and, it was observed 1.8 times more often in PTB/HIV+ patients than in PTB/HIV- patients (56.1% and 31.6% of all persons with positive sputum smear microscopy). It was characteristic of men, but not of women, in whom low MbT excretion was noted both in PTB/HIV+ (30.4%) and in PTB/HIV- (32.7%).

Frequency of extremely intensive MbT excretion was often comparable in PTB/HIV+ and PTB/HIV- patients (6.2% and 5.6% of all persons discharging MbT, respectively;

p>0.1). Nevertheless, this statement does not completely reflect the existing situation due to significant gender differences: extremely intensive MbT excretion was noted 1.5 times less often in MbT+ men with PTB/HIV+ than in MbT+ men with PTB/HIV-. A reverse situation was observed in women; extremely intensive MbT excretion was noted 4.1 times more often in MbT+ women with PTB/HIV+ than in similar women with PTB/HIV-. Gender differences in frequency of extremely intensive MbT excretion may be explained by various hypotheses requiring further testing; for instance, by the fact that among PTB/HIV+ women there might be a higher rate of injection drug users and that they care less about their health. The hypothesis requires further testing on the basis of another data set.

MbT excretion detected in culture examinations was noted slightly (1.2 times) more often in PTB/HIV+ patients in comparison with PTB/HIV- patients. Despite the fact that the differences were statistically significant, their epidemiological value is not high.

Low MbT excretion detectable only by culture method was observed 1.3 times more often in new patients with PTB/HIV+ (both in men and in women) in comparison with PTB/HIV-.

The proportion of paradoxical results of culture examination, when MbT was isolated by smear microscopy method but showed no growth, was comparable, 9.2% in PTB/HIV+ and 7.4% in PTB/HIV-.

To summarize, it may be noted that it is much more characteristic of TB/HIV patients to have tuberculosis at a younger productive (working) age while TB/HIV cases in children and elderly persons are extremely rare.

The same as in case of tuberculosis without HIV, women develop the disease at a younger age in comparison with men. The M/F ratio among tuberculosis patients with co-infection (new cases and relapse tuberculosis) is similar to that among all tuberculosis patients.

Among urban tuberculosis patients, the proportion of TB/HIV co-infection to all tuberculosis patients is higher than among rural tuberculosis patients.

Destruction of pulmonary tissue in tuberculosis patients with HIV-infection occur 1.3 times less often than in tuberculosis patients without HIV-infection; this is entirely characteristic of men, but not characteristic of women.

MbT excretion confirmed by smear microscopy method was slightly more often detected in pulmonary tuberculosis patients with HIV-infection than in similar patients without HIV-infection, though low MbT excretion (up to 9 AFB per 100 fields of view) was relatively more characteristic of patients with HIV-infection. Extremely intensive MbT excretion (3+) occurred less often in MbT+ men with HIV-infection than in MbT+ men without it, though the reverse was true for women.

Moreover, low MbT excretion detectable only by culture method but undetectable by smear microscopy was slightly more often observed in patients with pulmonary tuberculosis and HIV-infection.

Chapter V

Drug resistance of mycobacterium tuberculosis in TB/HIV patients

V.B. Galkin, S.A. Sterlikov, A.E. Zelenina, O.G. Zyryanova, Y.S. Kononenko, I.V. Kustova, P.A. Milyutina, O.V. Ovsyankina, O.A. Ovchinnikova, N.I. Pankova, N.D. Pirogova, O.A. Podgainaya, A.K. Svicharskaya, Y.A. Yukhnova, R.S. Yarullina

High frequency of drug-resistant tuberculosis agent detection in patients with TB/HIV is noted by many researchers. The first cases of TB with multidrug resistance (MDR-TB) were particularly diagnosed in patients with tuberculosis associated with HIV-infection [14]. Nowadays, we observe the impact of TB/HIV co-infection on advance of tuberculosis with extensive drug resistance of MbT (XDR-TB) [10]. High frequency of drug-resistant tuberculosis is attributed to a number of factors:

- specific conditions of social environment conductive for infecting with drug-resistant strains of MbT from TB patients dwelling in this environment who failed or defaulted (Lost to follow up) treatment;
- a nosocomial transmission of MbT to immunocompromised patients;
- personal psychological characteristics that previously contributed to patient's getting infected with HIV and condition patient's insufficient compliance to treatment.

There might be also influence of other factors contributing to drug resistance development in immunocompromised patients; for example, inadequate tuberculosis prophylaxis with the use of isoniazid and rifampicin, a high frequency of fluoroquinolones usage for diseases of ENT organs typical of HIV-infection, and etc.

Our goal was to study drug-resistant tuberculosis among tuberculosis patients with HIV-infection and without it. The eligibility criterion was positive result of sputum culture examination and drug susceptibility test.

Primary drug-resistance is predominantly dependant on conditions of social environment conductive for patient's getting infected with drug-resistant strains of MbT; and acquired drug-resistance development is substantially influenced by the absence of patient's compliance to treatment which is also closely related to social factors. For the purpose of drug-resistance study, data on 4550 tuberculosis patients (4485 patients with pulmonary tuberculosis, 62 patients with respiratory tuberculosis of other localizations, and 3 patients with extrapulmonary tuberculosis) with available results of drug susceptibility test (DST) of MbT to antituberculosis drugs were analyzed. The main group consisted of 647 tuberculosis patients with HIV-infection (TB/HIV+): 487 men and 160 women; 16 of them under 24 years of age; 213 – 25 to 34 years; 318 – 35 to 44 years; 74 – 45 to 54 years; 19 – 55 years and older; and data on age were not available for 7 patients. New tuberculosis cases were registered in 288 patients of the main group; relapse tuberculosis was registered in 78 patients. 281 patients of the main group received chemotherapy courses (ChT) as retreatment, including 205 patients receiving treatment after failure (TAF). The

control group included 3903 TB patients without HIV-infection (TB/HIV-): 3038 men and 865 women (table 5.1).

Table 5.1

Age and gender characteristics of the main and control groups.

		abs. number	Age groups (years)						Gender	
			< 24	25-34	35-44	45-54	> 54	N/A	Men	Women
Total of TB patients	HIV+	647	16	213	318	74	19	7	487	160
	HIV-	3903	191	899	1082	860	757	114	3038	865
New tuberculosis patients	HIV+	288	5	109	127	30	10	7	212	76
	HIV-	1932	119	472	481	393	396	71	1441	491
Relapse tuberculosis patients	HIV+	78	1	18	48	11			60	18
	HIV-	425	10	74	113	105	110	13	359	66
Patients with retreatment ChT	HIV+	281	10	86	143	33	9		215	66
	HIV-	1546	62	353	488	362	251	30	1238	308
including those after failed ChT treatment	HIV+	205	7	57	107	27	7		159	46
	HIV-	1158	56	246	375	273	198	10	924	234

Results of DST in new tuberculosis patients and in patients with relapse tuberculosis are presented in figure 5.1. An increase of MDR (exclusive of XDR) detection frequency is noted in the presence of HIV-infection.

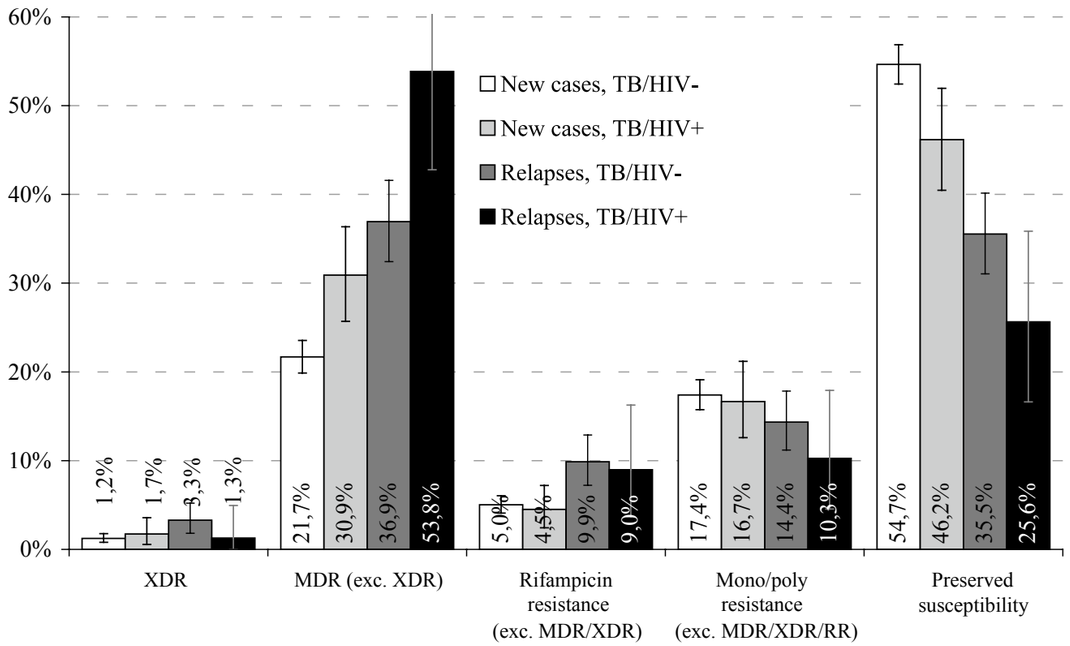

Figure 5.1. Results of DST in tuberculosis patients (new cases and relapses) with and without HIV-infection.

Primary MDR (exclusive of XDR) was 21.7% in tuberculosis patients without HIV-infection and 36.9% in patients with relapse tuberculosis while it was significantly higher in those with HIV-infection: 30.9% and 53.8%, respectively. XDR was observed in 1.2 to 3.3% of cases in these groups (p>0.05).

Proportion of patients with preserved drug susceptibility decreased in the presence of HIV-infection: the proportion of new TB/HIV+ patients with preserved drug susceptibility was 46.2%, and the proportion of TB/HIV+ relapses with preserved drug susceptibility was only 25.6%.

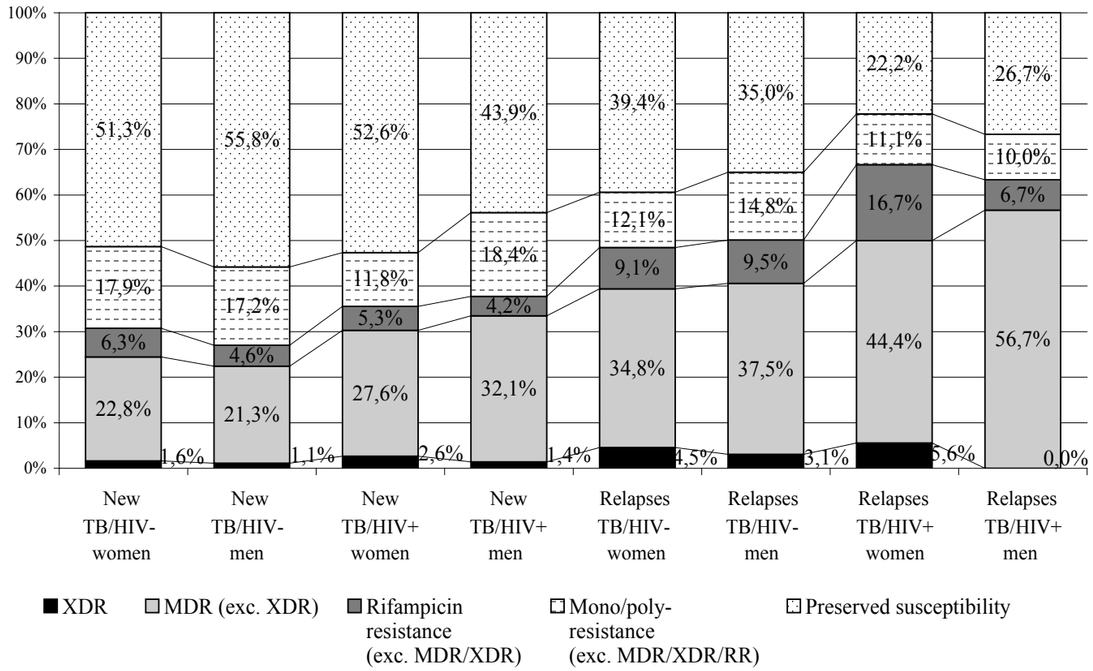

Figure 5.2. Results of DST in new patients and in relapse tuberculosis cases with and without HIV-infection by gender subgroups.

Figure 5.2 presents results of DST by gender subgroups in new TB patients and in relapse tuberculosis cases with and without HIV-infection. There are no significant differences in frequency of drug resistance in the main and control groups among men and women.

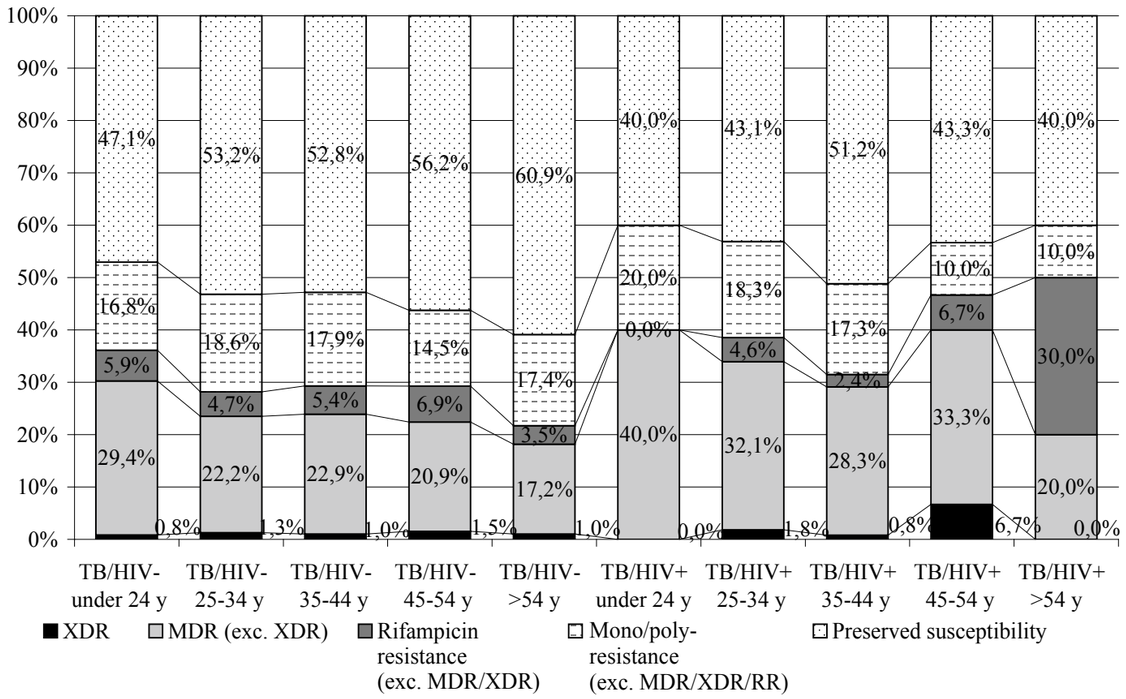

Figure 5.3. Results of DST in new tuberculosis patients with and without HIV-infection by age subgroups.

In age subgroups, a tendency of increase in proportion of patients with preserved susceptibility with age (from 47.1% in the under 24 years group to 60.9% in the over 54 age group ($p<0.01$)) is noted in new TB patients (Figure 5.3) of TB/HIV- group. In patients with relapse tuberculosis, a similar tendency was observed with increase of the proportion from 30.0% to 40.0%; however, there is a high possibility of this statement to be a statistical error ($p>0.05$).

In HIV-infected patients with relapse tuberculosis, subgroups under 24 years of age and over 54 years of age were not evaluated due to small sample size. The highest proportion of patients with preserved susceptibility was noted in the 25-34 age group (44.4%) which is significantly higher than in the 35-44 age group (20.8%, $p<0.05$), and this proportion reduced to 18.2% in the 45-54 age group.

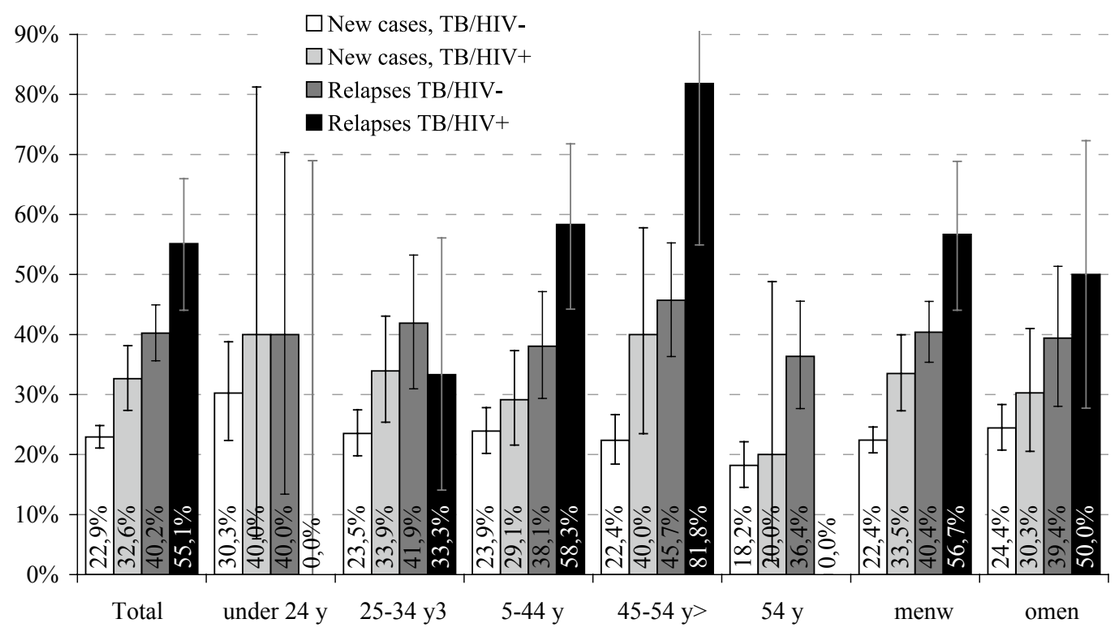

Figure 5.4. Proportion of MDR-TB patients (new TB cases and relapses) with and without HIV-infection by age and gender groups.

The study of the proportion of TB patients with detected multidrug resistance, including extensive drug resistance (MDR-TB), showed significant increase in this indicator in the presence of HIV-infection both in new tuberculosis patients (from 22.9% to 32.6%) and in patients with relapse tuberculosis (from 40.2% to 55.1%); though, these differences were characteristic only of men in whom the proportion of patients with primary MDR-TB increased from 22.4% (in TB/HIV-) to 33.5% (in TB/HIV+) in the presence of HIV infection and, in case of relapse tuberculosis, from 40.4% (in RTB/HIV-) to 56.7% (in RTB/HIV+), see Fig. 5.4. In women, the presence of HIV-infection did not bring on statistically significant growth of proportion of patients with MDR-TB.

In TB/HIV- patients, a decreasing tendency of MDR-TB detection rate (from 30.3%, in the age group of under 24, to 18.2%, in the age group of 55 and older ($p<0.05$)) was noted. On the contrary, in subgroup of relapse RTB/HIV+, the lowest level of resistance, 33.3%, was observed in the age group of 25-34, and it reached 81.8% ($p<0.05$) in the age group of 45-54. In other groups, no significant age-dependant change of MDR-TB rate was observed.

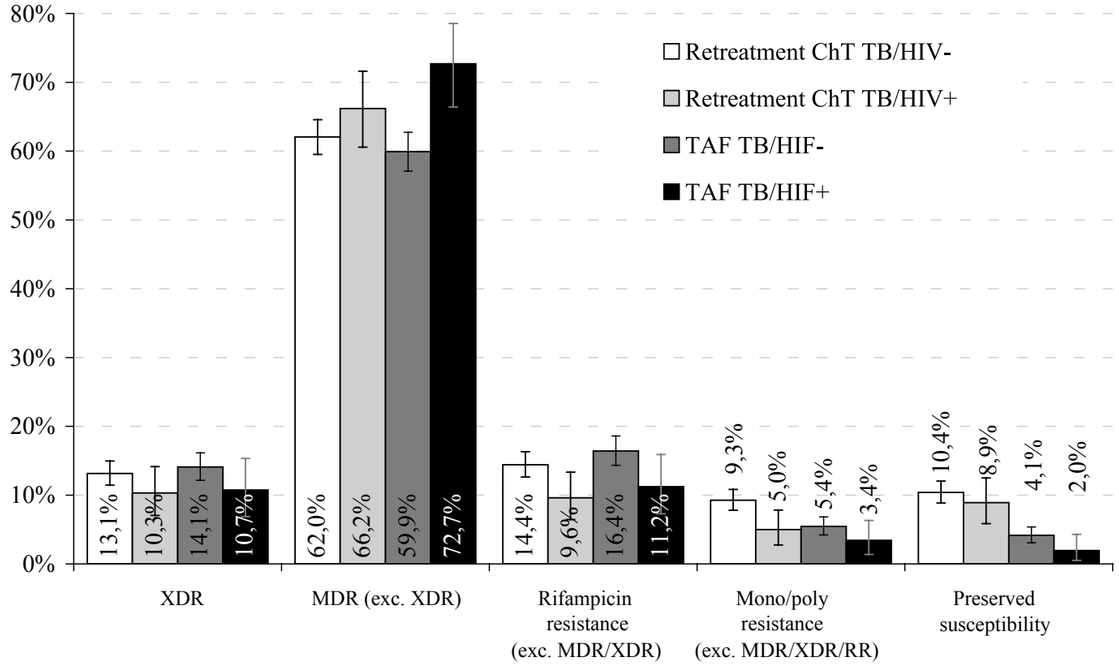

Figure 5.5. Results of DST in tuberculosis patients in retreatment cases (excluding relapses), including those receiving treatment after failure (TAF), with and without HIV-infection.

In retreatment cases (excluding relapses), the proportion of TB patients with extensive drug resistance exceeds 10% in all groups without significant differences in patients with and without HIV-infection (Figure 5.5). The detection rate of rifampicin resistance without MDR/XDR (RR) and mono/polyresistance (exclusive of RR/MDR/XDR) was higher in the presence of HIV-infection (14.4% and 9.3% in TB/HIV+, respectively) than in the absence of HIV (9.6% and 5.0%, in TB/HIV-, respectively; $p<0.05$).

At the same time, MDR-TB rate (excluding XDR) proved to be the highest, 72.7%, in cases of treatment after failure of patients with TB/HIV+ which is significantly higher than in patients with TB/HIV- (59.9%, $p<0.05$).

The proportion of patients with preserved drug susceptibility in retreatment cases (excluding relapses) was 8.9-10.4%, with and without HIV-infection. It should be noted that the minimal level of this parameter was observed in cases of treatment after failure: it was 4.1% in patients without HIV infection and 2.0% in those with HIV-infection ($p<0.05$).

Figure 5.6 presents results of DST in retreatment cases (excluding relapses) of TB patients, including treatment after failure, with and without HIV-infection by gender subgroups. No significant differences in the rates were noted in the main and control groups in men and women.

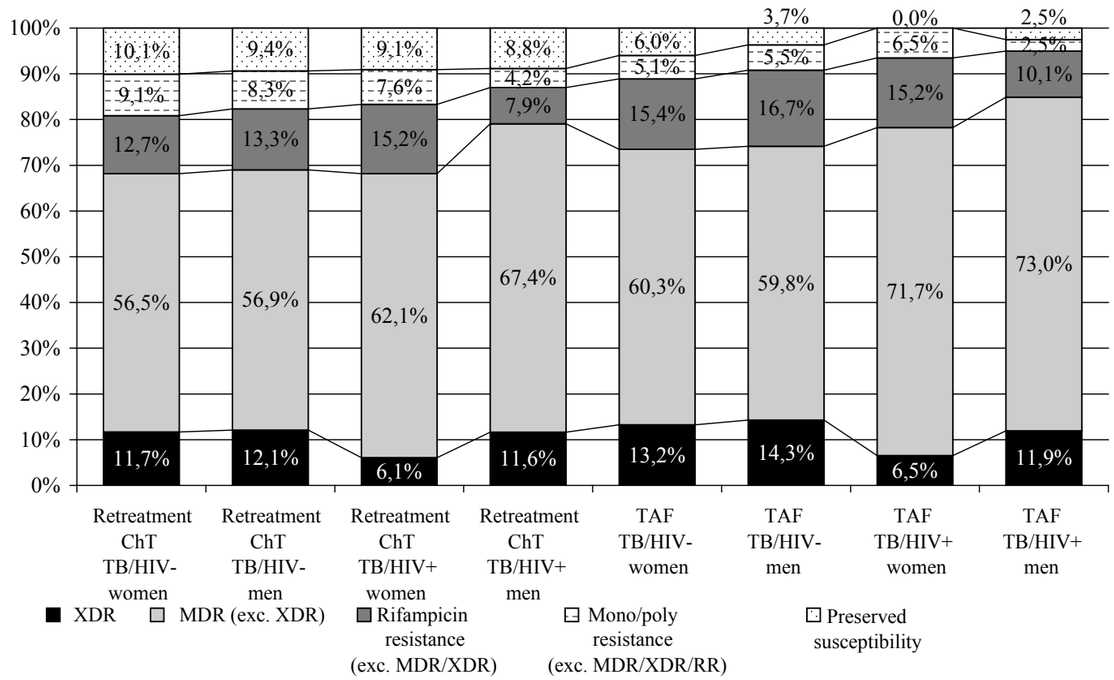

Figure 5.6. Results of DST in tuberculosis patients in retreatment cases (excluding relapses), including treatment after failure (TAF), with and without HIV-infection by gender subgroups.

In age subgroups, the tendency of increase of the proportion of patients with preserved susceptibility with age was also noted in retreatment cases (excluding relapses) TB/HIV- subgroups (Figure 5.7). For instance, in the age group of over 54, the proportion was 13.1%, which was much higher than in age subgroups of 25-34 and 35-44 (7.9% and 8.0% ($p<0.05$)). There were no significant tendencies in age subgroups of TB/HIV+ group.

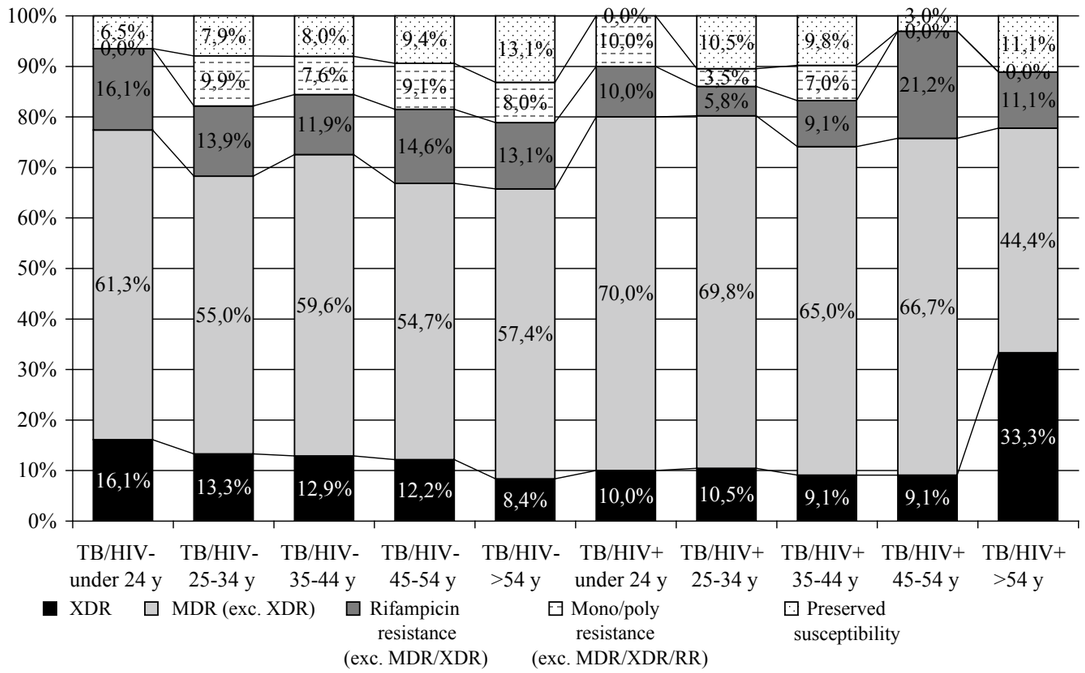

Figure 5.7. Results of DST in tuberculosis patients in retreatment cases (excluding relapses) with and without HIV-infection by age subgroups.

Figure 5.8 illustrates that MDR-TB is much more often detected in TB/HIV co-infected retreatment cases (excluding relapses): 76.5% in TB/HIV+, and 68.8% in TB/HIV- ($p<0.05$), and it is especially clearly seen in cases of treatment after failure (83.4% in TB/HIV+, and 74.0% in TB/HIV+, $p<0.05$). Though, it should be noted that this tendency is characteristic only of men (in retreatment cases (excluding relapses), 79.1% in TB/HIV+, and 69.0% in TB/HIV-, respectively; including cases of treatment after failure, 84.9% in TB/HIV+, and 74.1% in TB/HIV-; $p<0.05$) with no significant differences in women.

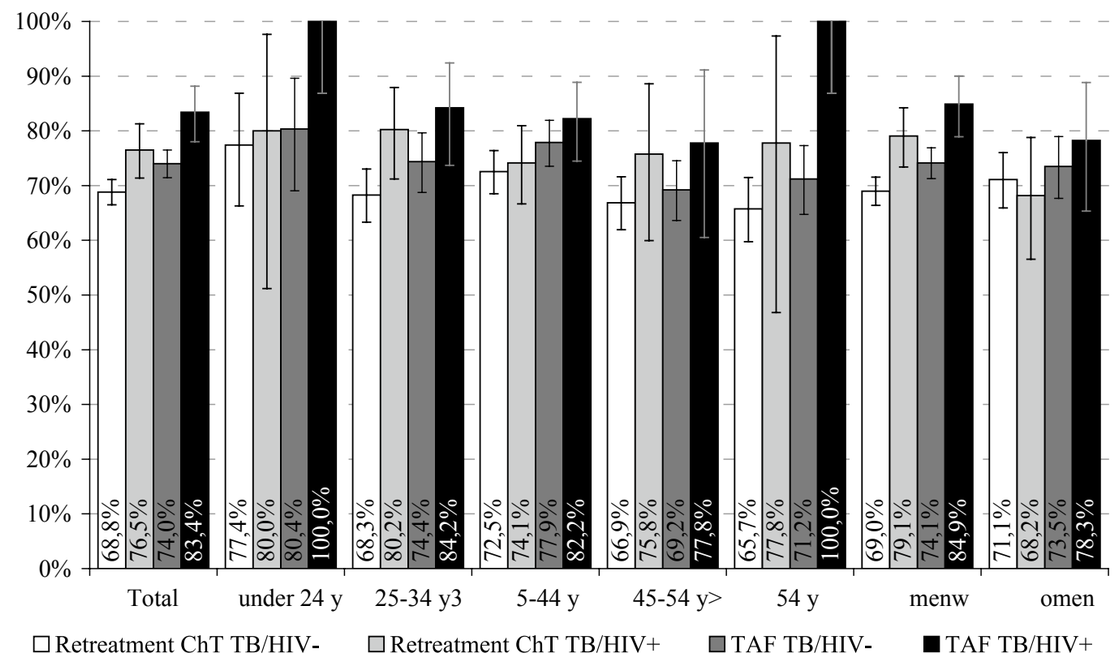

Figure 5.8. The proportion of TB patients with MDR-TB detection registered for retreatment cases (excluding relapses), including treatment after failure, with and without HIV-infection by age and gender.

The ratio of MDR-TB proportions in retreatment cases (excluding relapses) has no significant differences in the majority of age groups except for the 25-34 age group, where MDR-TB is more often detected in TB/HIV+ than in TB/HIV- (80.0%, and 68.3% of cases, respectively; $p<0.05$). In tuberculosis patients receiving treatment after failure, the proportion of MDR-TB reaches its maximum values (100%) in the outermost age groups, under 24 and over 55, in the presence of HIV-infection and 80.4%, and 71.2% ($p<0.05$) in the absence of HIV, respectively.

Thus, while prescribing both primary and repeated courses of treatment, especially after treatment failure in the younger and older age groups, it should be taken into account that the presence of HIV-infection in male patients elevates the risk of drug resistance TB. Though, it is not characteristic of female patients. In the absence of HIV-infection in tuberculosis patients, a tendency of increase of proportion of patients with preserved susceptibility of MbT was observed in the older age subgroups.

Chapter VI

Treatment outcomes in new patients with TB/HIV

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Combination of tuberculosis and HIV-infection undoubtedly has negative influence on the results of treatment in tuberculosis patients [7, 11]. Forms of statistics contain not data on results of treatment of patients with tuberculosis associated with HIV-infection, though there are single studies based on regional registers of TB patients containing data on this issue [5].

Our aim was to compare treatment outcomes in new tuberculosis patients with HIV-infection and without it. Results were stratified by gender and age.

5820 new tuberculosis patients (without post mortem cases) registered for treatment were enrolled in the study, including: 3907 men and 1913 women of the following age groups: under 17 – 239, 18-24 – 304, 25-34 – 1443, 35-44 – 1493, 45-54 – 952, 55-64 – 730, 65 and older – 425, N/A – 234. The main group comprised 669 tuberculosis patients with HIV-infection (TB/HIV+). 5151 tuberculosis patients without HIV-infection were included in the control group (TB/HIV-). Gender and age distribution of TB/HIV+ and TB/HIV- patients is shown in table 6.1.

Table 6.1

Age and gender characteristics of new tuberculosis patients.

		abs. number	Age groups (years)						Gender	
			< 25	25-34	35-44	45-54	≥ 55	N/A	Men	Women
Total of new tuberculosis patients	HIV+	669	19	245	300	69	18	18	458	211
	HIV-	5151	524	1198	1193	883	1137	216	3449	1702
including: cases of canceled TB diagnosis	HIV+	5	0	0	4	1	0	0	5	0
	HIV-	195	5	24	30	36	99	1	129	66
transferred to the MDR regime	HIV+	133	7	48	54	14	5	5	94	39
	HIV-	679	72	165	179	129	91	43	470	209
Chemotherapy treatment carried as susceptible TB	HIV+	531	12	197	242	54	13	13	359	172
	HIV-	4277	447	1009	984	718	947	172	2850	1427

Diagnosis of tuberculosis was canceled in 200 (3.4%) patients. The rate of canceled diagnosis increased in older age subgroups: it was 1.6-1.7% in the age groups of 18-24 and 25-34; 2.3% in the age group of 35-44; 3.9% – 45-54; 7.9% – 55-64, and reached 9.6% in the age group of 65 and older. This tendency was not noted among 669 patients with HIV-infection; and cases of canceled diagnosis were registered much more rarely, in 5 patients only (0.7%), in the age group of 35 to 54.

Out of 5620 tuberculosis patients with confirmed diagnosis, 812 patients (14.4%) were transferred to the MDR regime; what's more, transferring to the MDR regime was done much more often in case of HIV-co-infection (664 patients), 20.0% of cases (133 patients), than without it, 13.7% (679 cases, $p<0.001$). In tuberculosis without HIV-infection, moderate maximum of frequency of transferring to the MDR regime is observed in the middle age groups of 18 to 54, 14.1-15.5%, while the proportion of patients transferred to the MDR regime exceeds 33% in TB/HIV+ in the subgroups of under 24 and 55-64 years of age (Fig. 1). In men, transferring to the MDR regime is more often noted in tuberculosis associated with HIV-infection (20.8%) than without it (14.2%, $p<0.001$).

Treatment outcomes were studied in 4808 treated patients with tuberculosis of different localizations, including: 4371 patients with pulmonary tuberculosis, and 437 patients with extrapulmonary tuberculosis of other localizations (258 – respiratory extrapulmonary tuberculosis and 179 – tuberculosis of other organs); 3209 men and 1599 women; in the age of: under 17– 209, 18-24 – 250, 25-34 – 1206, 35-44 – 1226, 45-54 – 772, 55-64 – 599, 65 and older – 361, age data not available – 185. Tuberculosis associated with HIV-infection was diagnosed in 531 patients, distribution of treated TB/HIV+ and TB/HIV- patients by age and gender subgroups is presented in table 6.1.

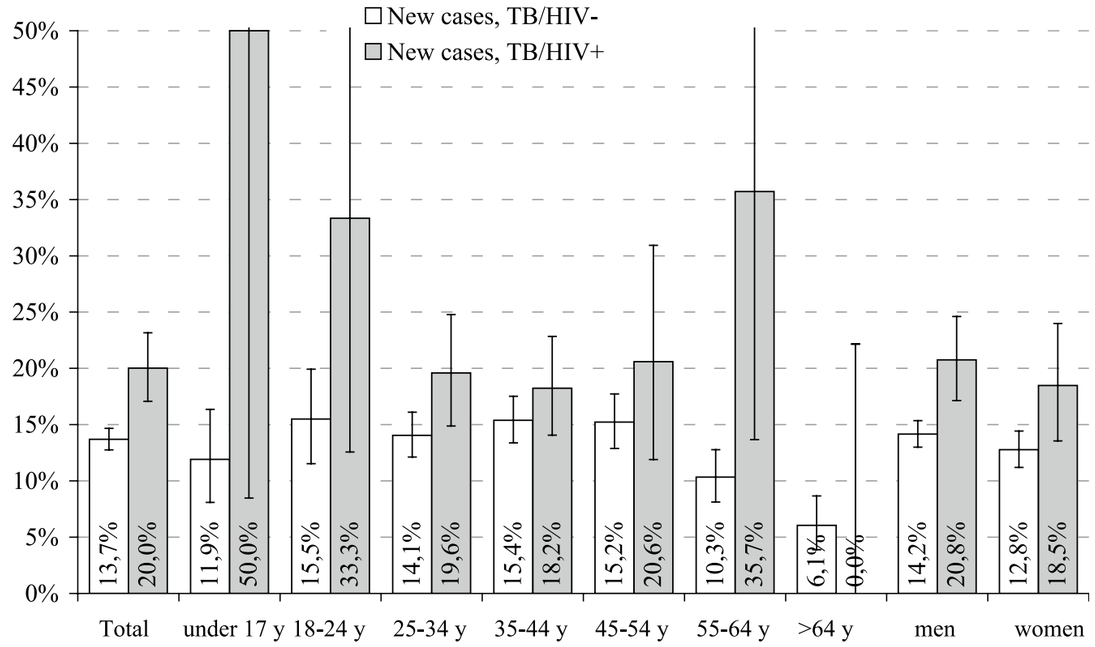

Figure 6.1. The proportion of TB patients transferred to the MDR regime with and without HIV-infection by gender and age.

Tuberculosis associated with HIV-infection significantly impairs treatment effectiveness in new patients: from 77.3% in TB/HIV- to 52.7% in TB/HIV+ ($p<0.001$), which can also be observed in gender subgroups and in the majority of age subgroups (Figure 6.2).

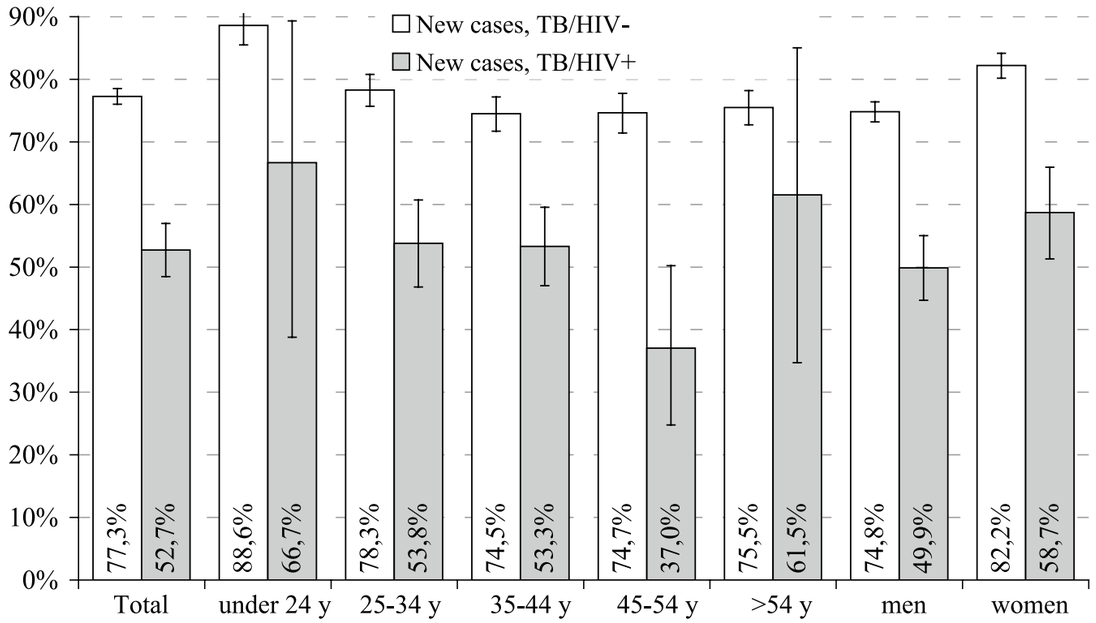

Figure 6.2. Treatment success rate of TB patients with and without HIV-infection by age and gender subgroups.

Treatment success rate was more often noted in extrapulmonary tuberculosis patients (79.9%) than in those with pulmonary tuberculosis (74.0%, $p<0.05$), but this tendency is characteristic of TB/HIV- patients only, both of men and women (Fig. 3). There were no significant differences in frequency of treatment success of pulmonary and extrapulmonary tuberculosis in TB/HIV+ patients.

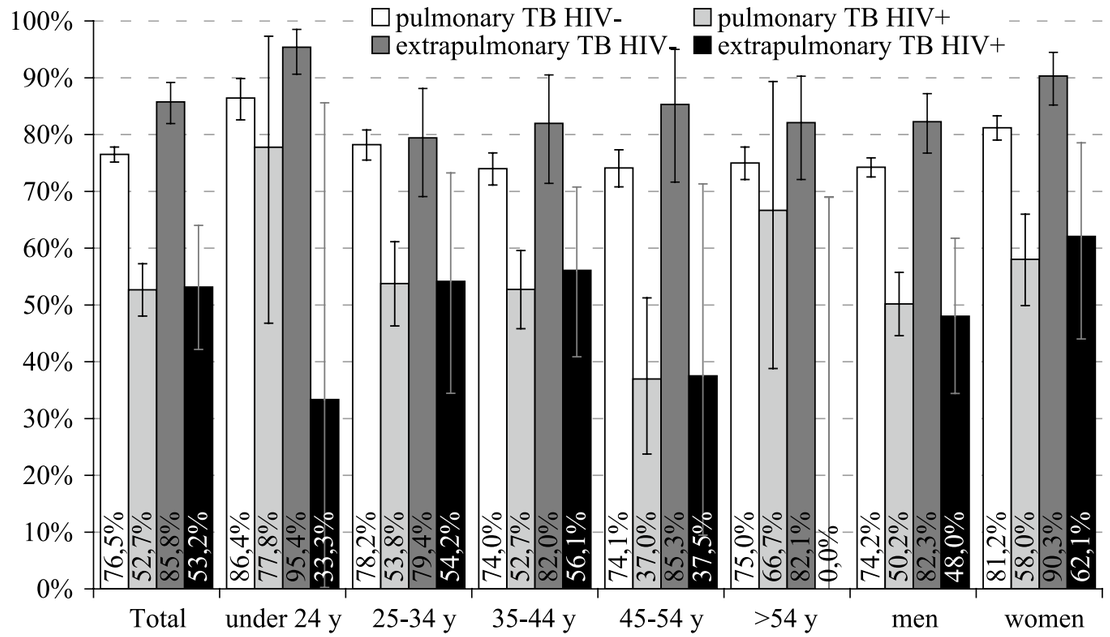

Figure 6.3. Treatment success rate in patients with pulmonary and extrapulmonary tuberculosis by age and gender subgroups.

Analyzing the structure of five unfavorable outcomes, taking their total number as 100% (Figure 6.4), it may be noted that in TB/HIV- cases, outcomes ChT treatment failure, Died from causes other than tuberculosis, and Defaulted (Lost to follow up) ChT treatment each was 22.0-22.3% of the unfavorable outcomes; Transferred out, 18.6%; and Died of tuberculosis, 14.7%. In group TB/HIV+, the proportion of outcome Died from causes other than tuberculosis sharply increases to 56.2% due to decrease of proportions of other outcomes: ChT treatment failure, 12.4%; Died of tuberculosis, 3.6%; Defaulted (Lost to follow up) ChT treatment, 17.5%; and Transferred out, 10.4%. All the differences in TB/HIV+ and TB/HIV- groups are statistically significant ($p<0.05$), and there were no significant differences in gender subgroups.

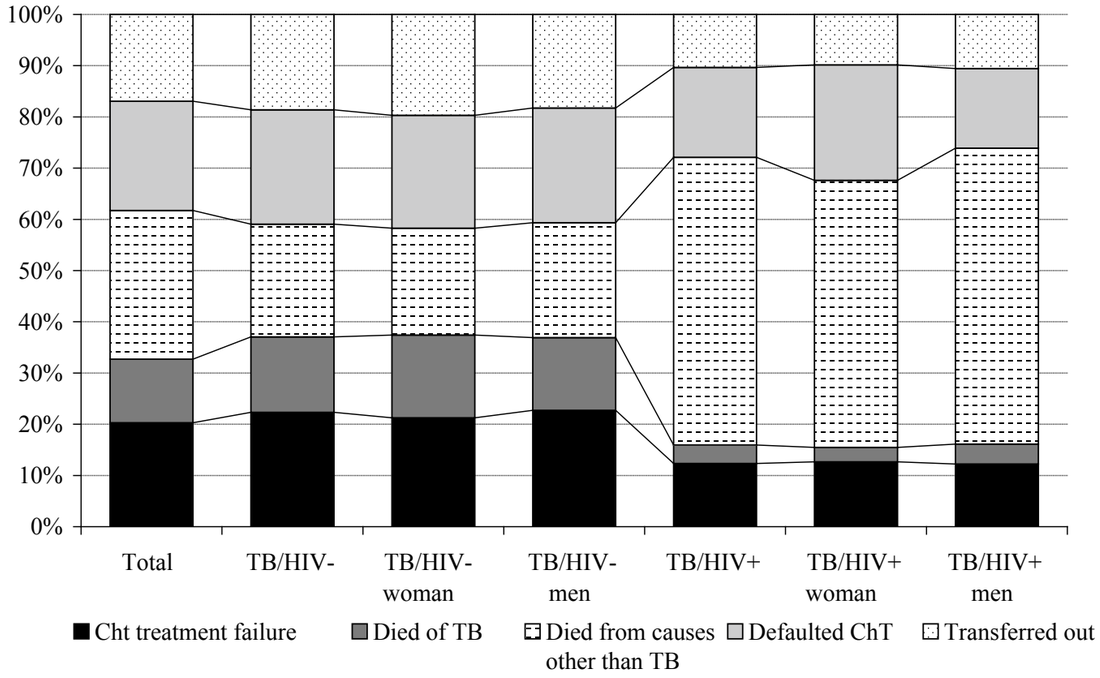

Figure 6.4. The structure of unfavorable treatment outcomes in tuberculosis patients with and without HIV-infection and by gender subgroups.

As for age subgroups (Figure 6.5) in TB/HIV+ and TB/HIV- groups, a general tendency of decrease in proportion of outcomes Transferred out and Defaulted (Lost to follow up) ChT treatment with age and increase in tuberculosis mortality is observed. The proportion of patients with TB/HIV- who died from causes other than tuberculosis reaches its maximum at the age of over 54, 33.2%, and, in TB/HIV+ patients, it exceeds 50% already at the age of 25-44 and is more than 60% in older patients. The decreasing tendency of the proportion of ChT treatment failure outcome with age is noted only in TB/HIV+.

The proportion of each of unfavorable treatment outcome was less than 6% in all treatment outcomes in the TB/HIV- group (Figure 6.6): ChT treatment failure, Defaulted (Lost to follow up) ChT treatment, and Transferred out were observed in 5.0-5.1% of cases; fatal outcome from causes other than tuberculosis was observed slightly less often (4.2%), and the frequency of their registration in men (5.6-5.7%, and 4.6%, respectively) was significantly higher than in women (3.7-3.9% and 3.5%, $p<0.05$). In comparison with other outcomes in TB/HIV-, lethality of tuberculosis was registered most rarely, 3.3% ($p<0.05$) without statistically significant differences between men (3.6%) and women (2.9%).

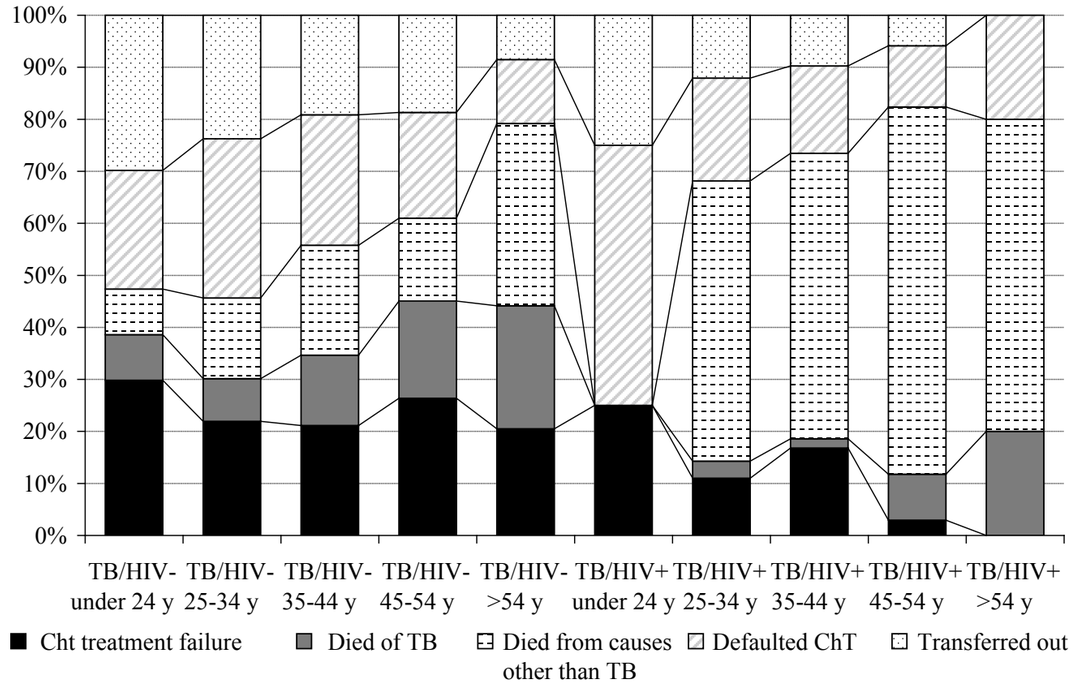

Figure 6.5. The structure of unfavorable outcomes of treatment in tuberculosis patients with and without HIV-infection by age subgroups.

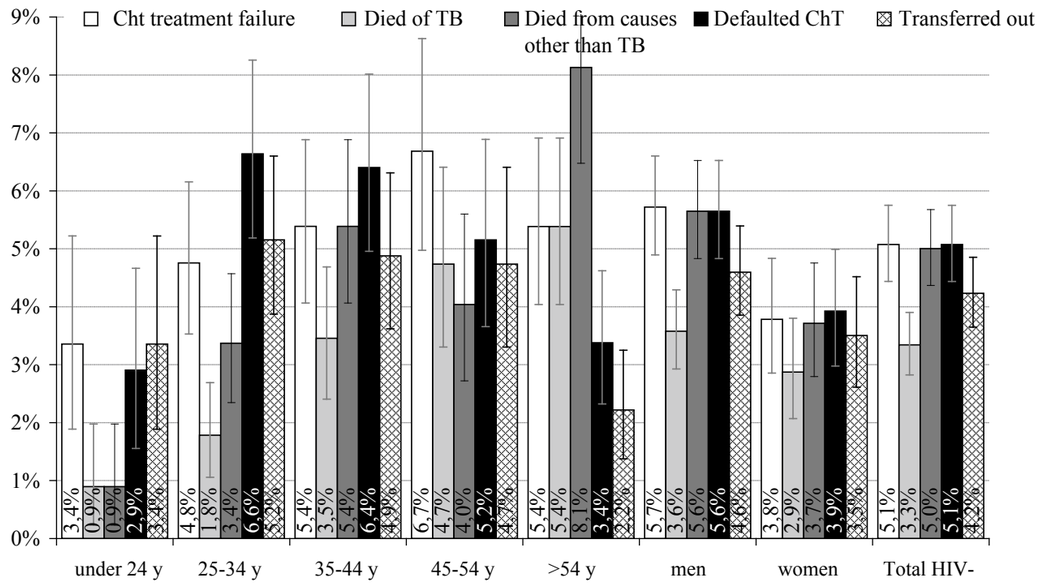

Figure 6.6. Frequency of unfavorable outcomes of treatment in tuberculosis patients without HIV-infection by age and gender subgroups.

Age trends are most clearly revealed in comparison of the 25-34 and over 54 subgroups. While in the subgroup of the younger age Defaulted (Lost to follow up) ChT treatment (6.6%) and Transferred out (5.2%) outcomes prevail, and the rate of fatal outcomes is low (1.8% – of tuberculosis and 3.4% – from causes other than tuberculosis), the rate reaches its maximum (5.4% and 8.1%, respectively) in the older age group with a low proportion of defaulted (lost to follow up) chemotherapy treatment course (3.4%) and transferred out patients (2.2%) ($p<0.05$).

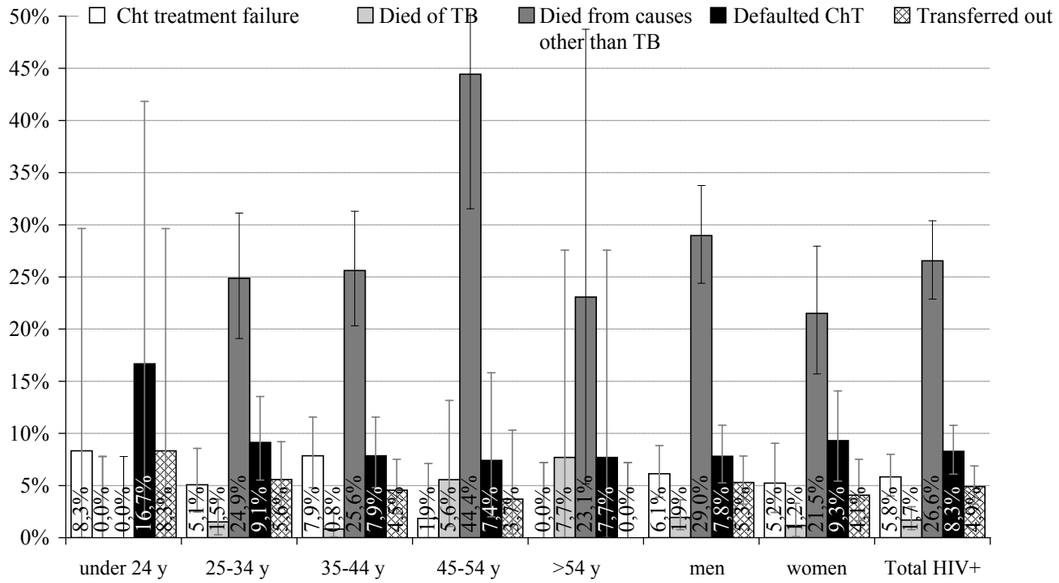

Figure 6.7. Frequency of unfavorable treatment outcomes in tuberculosis patients in the presence HIV-infection by age and gender subgroups.

In the presence of HIV-infection (Figure 6.7), lethal outcome from causes other than tuberculosis is indisputably in the lead ($p<0.05$) among unfavorable outcomes, 26.6% of treatment outcomes, including 29.0% in men, and 21.5% in women. The age maximum is observed in the age group of 45-54 (44.4%) which is higher than in younger subgroups ($p<0.05$). In TB/HIV+ age subgroups, decreasing tendencies in the proportion of defaulted (Lost to follow up) and transferred out cases with age are noted with increase of lethality of tuberculosis, which is similar with TB/HIV-; though, there is a high possibility of a statistical error ($p>0.05$).

Thus, as a conclusion of treatment outcomes study of new tuberculosis patients with and without HIV-infection in the context of gender and age stratification, the following should be pointed out:

- during registration of new patients for a treatment, the frequency of TB diagnosis being canceled increases with age (up to 9.6% in the age group of over 64), which is probably due to difficulties of differential diagnostics, primarily with oncological diseases. It is more rarely observed (0.7%) in the presence of HIV-infection, which is due to the necessity for more rapid diagnostic tactics in which the majority of cases of canceled tuberculosis diagnosis probably take place in the quarterly period, so they are not included in the enrolled cohort;
- transferring to the MDR regime of patients takes place more often (20.0%) in the presence of HIV-infection with maximum in subgroups of under 24 and 55-64 where the proportion of MDR exceeds 33%;
- treatment success rate is higher in patients with extrapulmonary tuberculosis (79.9%) than in patients with pulmonary tuberculosis (74.0%, $p<0.05$), and the tendency is characteristic only of TB/HIV-patients, including both men and women;
- tuberculosis associated with HIV-infection significantly impairs treatment effectiveness in new patients, from 77.3% to 52.7% ($p<0.001$), which may also be observed in gender subgroups and in the majority of age subgroups;
- in TB/HIV+ and TB/HIV- age subgroups, there is a general decreasing tendency with age in the proportion of outcomes Transferred out and Defaulted (Lost to follow up) with increase of proportion of patients who died of TB. The first fact is probably due to higher mobility and poorer treatment compliance of persons of younger age. In older persons, tuberculosis treatment is known to be complicated by various factors regardless of presence or absences of HIV-infection;
- in the presence of HIV-infection, the rate of lethal outcomes from causes other than tuberculosis is 26.6% with the age maximum observed in the age group of 45-54 (44.4%). It is known, that in such cases HIV-infection is most often registered as cause of death; and in the presence of HIV in the stage of AIDS, tuberculosis has the character of secondary infection.

Conclusion

Despite of apparent success in tuberculosis control, the stabilization of TB epidemic situation is not characterized by steadiness, primarily due to HIV-infection increase and high tuberculosis notification rate in HIV-infected persons. Unfavorable prognosis for the situation is aggravated by an increase in the proportion of patients with late stages of HIV-infection. The proportion of HIV-infected persons among tuberculosis patients is steadily increasing both in public healthcare facilities and in penitentiary facilities of Russian Federation. While in public healthcare TB/HIV notification rate is primarily defined by tuberculosis notification rate of population, in penitentiary facilities, it is predominantly defined by HIV-infection prevalence rate. The connection between TB/HIV notification rate and drug traffic as well as gender peculiarities of TB/HIV notification rate in vulnerable social groups can be clearly observed particularly in penitentiary facilities: women in correctional facilities get infected with TB/HIV almost as often as men.

The growth of TB/HIV primarily threatens labor force of Russian Federation as new TB/HIV cases are registered mainly among persons of productive (working) age, which accounts for about 95% of all cases. The proportion of TB/HIV patients in tuberculosis patients is higher among urban residents.

During the analysis of clinical picture and special aspects of HIV-infection course, significant gender peculiarities were revealed which resulted in the necessity to consider study results for men and women separately.

An increased (1.8 times) rate of respiratory extrapulmonary tuberculosis is characteristic of new TB/HIV patients (both men and women). Moreover, an increased rate of extrarespiratory tuberculosis is characteristic of men, in contrast to women.

A lower rate of destruction of pulmonary tissue in new patients with pulmonary tuberculosis with HIV-infection was characteristic of men but not of women. Along with this, an increased rate of MbT excretion confirmed by smear microscopy was characteristic of TB/HIV patients, though TB/HIV patients were more often characterized by low intensity of MbT excretion.

Among new male TB/HIV patients, the proportion of cases with preserved drug susceptibility of MbT is lower, and the proportion of patients with primary multidrug resistance is higher. This suggests that a certain part in the increase of the risk of MDR-TB in this group may be the factor of presence in the social environment where there are also MDR-TB patients. This factor is irrelevant in new female TB/HIV patients.

Interestingly, the possibility of detection of tuberculosis without HIV infection with preserved drug susceptibility became higher with a patient's age increase, which completely reflects the higher possibility of initial infecting of older persons (which most likely took place in earlier years) with susceptible strains of the MbT. In TB/HIV patients, no such tendency was observed. This can be ascribed to a higher possibility of superinfection which took place in the recent epidemic situation in conditions of high prevalence of drug-resistant tuberculosis. The significant influence of superinfection in TB/HIV patients is indicated by a higher rate of MDR-TB in cases of retreatment of patients with TB/HIV than that of patients with tuberculosis without HIV-infection (the differences are not statistically significant for women). The higher rate of drug resistance in male TB/HIV patients should be taken into account when prescribing treatment.

In 2017, the Russian Federation submitted data on treatment results of TB patients (new cases and relapse tuberculosis) for the WHO Global Tuberculosis Report for the first time. In regards treatment success rate, the Russian Federation shows in general the same results as the WHO European region but mortality rate in TB/HIV patients is higher than in the European region and worldwide.

Upon detailed study of treatment outcomes, it was found that, the combination of tuberculosis with HIV-infection reduces the rate of treatment success rate (in our study by 1.5 times) both in the Russian Federation and worldwide.

Both in TB/HIV patients and in cases of tuberculosis without HIV-infection, there is a tendency of the proportion of patients who prematurely discontinued treatment to decrease with age, while the proportion of patients who died of tuberculosis increases with age. This may be due to a higher mobility and poorer treatment compliance of persons of a younger age. In the presence of HIV-infection, the rate of lethal outcomes from causes other than tuberculosis is more than 25% of outcomes with the age maximum observed in the age group of 45-54 (almost half of outcomes). It is known, that in such cases HIV-infection is most often registered as cause of death, and in the presence of HIV in stage of AIDS, tuberculosis has the character of secondary infection.

In conclusion, we'd like to express our appreciation to all study participants, including those who are not amongst its authors but who contributed to it. We hope that the study results will be of use in practical activities of each specialist.

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