

The Situation of HIV/*M. tuberculosis* Co-Infection in Russia

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Abstract: This report details the main findings of research of latest available data concerning epidemiological status of human immunodeficiency virus/ acquired immunodeficiency syndrome (HIV/AIDS) and *M. tuberculosis* (MTB) infections as well as HIV/MTB co-infection in support of Russian Federation (RF) Country Report for the EUCO-Net project on global cooperation in the field of HIV and MTB. In addition to epidemiological analysis this report presents the list of publications concerning epidemiological researches of referred above infections in RF and some other information. The research was undertaken in the period from 2008 to March 2010. The report concludes that the number of tuberculosis (TB) patients with HIV in RF is not great, but is rapidly growing and enhancement of efforts directed on fight against this co-infection are crucially needed.

Keywords: Russia, HIV/*M. tuberculosis* co-infection, HIV, tuberculosis, HIV subtype A1, new outbreaks.

BACKGROUND

Co-infection with multiple pathogens represents a major threat to human health on a global scale. One of deadly combination is the co-infection HIV with MTB [1,2]. It is estimated that approximately one quarter (11 million) of the global population infected with HIV are co-infected with MTB [3]. The problem consists that the background of HIV results in immune dysfunction that leads to the reactivation from latent to active tuberculosis or to increase the likelihood of developing active disease after exposure to MTB bacilli. As a consequence, TB-mortality is about four-fold higher amongst HIV-seropositive than in seronegative patients [4]. Epidemiological situation of HIV/MTB co-infection illustrates the dimension of the associated health problems. In general, MTB and other *Mycobacteria* are the most common HIV-related opportunistic infection worldwide and represent the leading cause of mortality in HIV-infected patients, both in adults and children [5]. Management of this public health problem is further complicated due to difficulties with the early diagnostics active TB especially in HIV-infected patients because conventional skin tests as a rule yield the negative outcome on the background of depressed immunity [6]. One more relevant problem is the complex interactions between antiviral and antibacterial therapy. Vivid example is immune reconstruction inflammatory syndrome (IRIS), which is characterized by clinical deterioration during anti-retroviral therapy (ART) that is thought to be due to an immunopathological reaction to MTB as MTB-specific immune response improve [7].

It is obvious that there is urgent necessity for increased knowledge of the pathogenesis HIV/MTB co-infection and intensified research to explore ways to reduce TB transmission and TB reactivation in people with HIV [8].

Several international and domestic efforts have been made in Russia over the last time to control this dual epidemic. Some success has been achieved, but much more needs to be done.

DEMOGRAPHIC SITUATION IN THE RUSSIAN FEDERATION

The last population census in RF was passed in 2002 (www.perepis2002.ru). By its outcomes, the permanent population has compounded 145.3 million persons, but after that quantity of citizens was diminished to 141.9 million persons by the first half of 2009. According to Federal State Statistics Service (FSSS) of RF (www.gks.ru) for 1 January 2010 the population has compounded 141297 thousands persons [9]. Besides, according to Federal Migratory Service (FMS) of RF (www.fms.gov.ru) annually 20 million labour migrants comes to RF [10].

The estimated death rate in RF for 2009 is 14.2 persons per 1000 against the world average of 9 per 1000. The annual birth rate is 12.4 per 1000 (FSSS). The population of RF is significantly urbanized. According to census of 2002, 73% of Russians are city dwellers, 27% - villagers. Also, the significant prevalence of quantity of women in comparison with quantity of men (53.4% of women in overall population) that typical to Russia has been recorded. In addition, the excess of number of aged persons over number of children (18.1% of children in overall population, 61.3% - working-age population, 20.5% - older an able-bodied age) has been registered.

EPIDEMIOLOGICAL ANALYSIS

The research examined the most up-to-date epidemiological data released by the World Health Organization (WHO, www.who.int) [11], the Joint United Nations Programme on HIV/AIDS (UNAIDS, www.unaids.ru, www.unaids.org) [12], United States Agency for International Development (USAID, www.usaid.gov) [13], Russian Federal AIDS Center (RFAC, www.hivrussia.org) [14] and Russian

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TB incidence and mortality in Russia (per 100 000 of population)

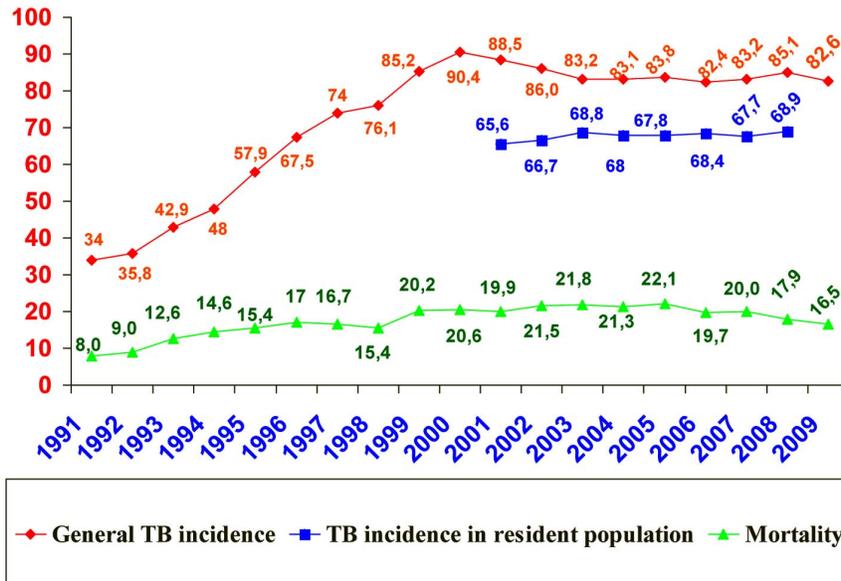


Fig. (1). TB incidence and mortality in Russia (per 100 000 of population).

Ministry of Health and Social Development (MoH & SD RF, www.minzdravsoc.ru) [15].

Basic Epidemiological Data on TB

Substantial changes regarding registered TB incidence were noted in Russia in the last 20-25 years. Gradual decrease of incidence rate till 34,0 per 100 thousand population in the years 1970-1980 changed to considerable growth during 1991 to 2000 and reached 90,7 (2,7 times more) with subsequent stabilization in the first years of the new century at the level of 82-84 per 100 thousand population (see Figs. 1, 2) [16].

TB prevalence among the population is an important cumulative indicator of an overall performance on treatment and surveillance efficiency of TB patients.

TB prevalence rate which is the important indicator of the epidemiological situation is defined as the number of patients, who at the end of the year are still considered to be TB patients per 100 thousand populations [17].

Recently close attention has been paid to the problem of MDR-TB prevalence. High level of MDR-TB makes serious impact on TB spread by way of accumulating of sources of infection in population because of treatment efficiency decrease. Fast spread of HIV infection in Russia affects TB prevalence rate as well.

Today in Russia for TB control the extensive indicators showing the share of MDR-TB patients among various types of patients are used.

HIV infection in Russia has been registered since 1987 [18]. Since then TB has been revealed in HIV-infected patients. The data on TB-cases among HIV-infected has been included in state statistical surveillance form since 1999.

Introduction of unified record and coordination of TB aid to HIV-infected patients affected increase of registered cases with associated infection [19].

Coverage by screening examination of HIV infection out of new TB patients in 2007 made 90,9%.

The all-Russian prevalence indicators on TB associated with HIV infection reflect only the situation in Russia on the whole while the data from separate subjects of federation (regions) can differ considerably from each other and from the all-Russian data as well [20] (Table 1).

Risk groups number makes essential impact on TB epidemiological indicators too. In Russia distinguish 2 risk groups:

Social: homeless; refugees; migrants; being in or released from penitentiary institutions; persons living in shelters, doss-houses, retirement homes; patients in narcological and psychiatric institutions.

Medical: HIV-infected patients, patients with professional lung diseases because of dust, pancreatic diabetes, peptic ulcer (including operated patients), patients receiving corticosteroid, cytostatic or radiological therapy, patients with radiographic posttuberculous changes.

In accordance with the order of MoH & SD RF the persons from the risk groups undergo additional annual TB examination, however this is not always possible because of their social vulnerability.

The data on TB patients results on the DOTS strategy recommended by WHO is presented in Table 2. DOTS strategy has been adapted to the conditions of Russia and implemented in all regions of Russia according to the order of MoH & SD RF since 2003. According to the reporting

Table 1. Basic Epidemiological Data on TB in the Russian Federation in 2007

	TB/HIV Prevalence	TB/HIV Incidence (Per 100 Thousand Population, Detected in Reporting Year)	TB Prevalence (Per 100 Thousand Population)	TB Incidence (Per 100 Thousand Population)	MDR Prevalence Proportion of MDR (%) Out of Registered TB Patients	MDR Incidence Proportion of MDR (%) out of New TB Patients	XDR Out of New TB Patients *	XDR Out of Previously Treated *
Cumulative population	8,2	4,2	194,5	83,2	21,4	9,75	1 out of 40 (3%)	24 out of 217 (11%)
Resident population	7,4			67,7				

*Resistance rate to second-line drugs was surveyed among 257 patients with MDR-TB from Orel and Vladimir regions, registered in 2006. 25 (10%) patients out them were XDR-TB positive, including 1 (3%) out of 40 new TB patients and 24 (11%) out of 217 previously treated patients.

Table 2. TB Patients Treatment Results on the DOTS strategy in the Russian Federation (Cohort Analysis)

	Proportion of Patients with Successful Treatment Out of All Patients with Treatment Completed (%)	Proportion of Patients with Treatment Failure Out of All Patients with Treatment Completed (%)	Proportion of Patients with Treatment Outcome, Default (Interrupted) (%)	Proportion of TB Deaths (%)	Proportion of Deaths (Other Reasons) (%)	Proportion of Discharged Patients (%)
Russian Federation	58,2	14,5	9,2	3,9	10,1	4,1

system accepted in RF on the treatment results, the analysis includes the data on the patients who have interrupted treatment, died (from TB and other diseases) and discharged patients (see Fig. 3).

In RF MDR-TB dissemination growth differs both in newly detected patients and earlier treated.

Extent of dissemination of MDR-TB differs substantially in different regions of RF.

HIV/AIDS Epidemic

The HIV/AIDS epidemic in RF is one of the fastest growing in the world. Many specialists consider Russia as a new epicenter in global HIV/AIDS pandemic (see Table 4). As of December 2009, there have been more than 516.167 officially diagnosed cases of HIV infection and 7.638 AIDS cases. It is widely acknowledged, however, that Russia's official statistics represent only a fraction of the actual number of HIV-infected Russians. Most experts estimate that

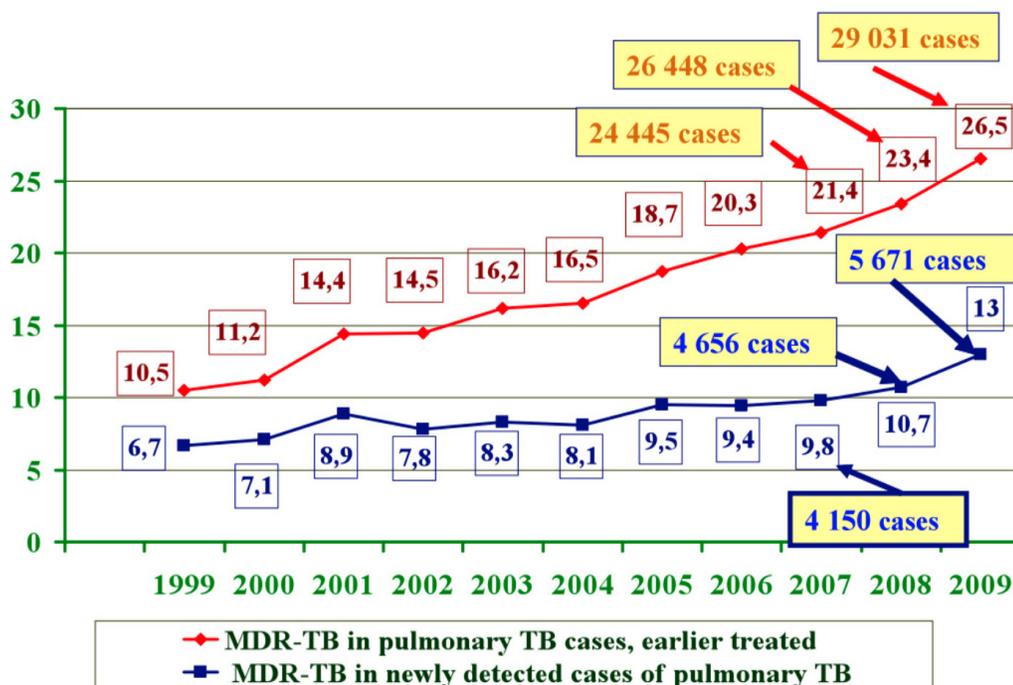


Fig. (2). MDR-TB (1999-2009) (%).

MDR-TB among all pulmonary TB cases in the Russian regions, 2009 (Rank-order (MDR-TB, 2009); Absolute number (at the end of the year) (per 100 000))

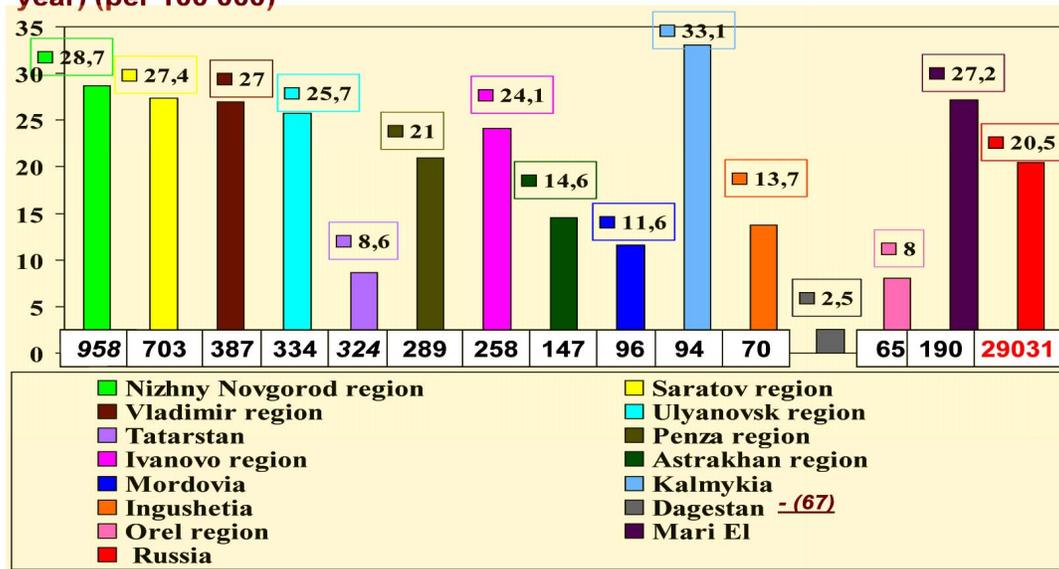


Fig. (3). MDR-TB among all pulmonary TB cases in the Russian regions, 2009 Absolute number (at the end of the year) (per 100 000).

Table 3. MDR-TB Patients Treatment Results on the DOTS+ Strategy in the Pilot Territories of the Russian Federation

Regions of RF	Proportion of Patients with Successful Treatment Out of All Patients with Treatment Completed (%)	Proportion of Patients with Treatment Failure Out of All Patients with Treatment Completed (%)	Proportion of Patients with Treatment Outcome, Default (Interrupted) (%)	Proportion of TB Deaths (%)	Proportion of Discharged Patients (%)
Arkhangelsk	40,7	13,1	32,6	13,1	0,3
Ivanovo	54,8	16,7	26,2	0	2,4
Orel	56,5	14	13	9,5	3
Tomsk	78,3	6,6	9,8	4,9	0,4

MDR-TB therapy in RF is carried out in the framework of the Project “MDR-TB diagnostics and treatment”. The projects “MDR-TB diagnostics and treatment”, which are financially supported by the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) are realized (or approved) in 21 administrative territories of RF and in 4 Federal TB institutes, where the Centers on drug resistant TB are operating. We consider worth-while in the framework of the report to extend evaluation criteria indicators “Treatment results of TB patients (excluding MDR-TB patients)”, “Treatment results of MDR-TB patients”. The epidemiological data presented in the report is for the year 2007 since the data for 2008 will be available only in March 2009.

Table 4. Present Trends in the Spread of HIV Infections and TB Disease

	HIV Prevalence in 2007	HIV Incidence in 2007 (new)	TB Prevalence in 2006	TB Incidence in 2006 (new)	MDR Prevalence in 2006	MDR Incidence in 2006 (new)	XDR Prevalence in 2006	XDR Incidence in 2006 (New)	Rate of Transmitted Drug Resistant HIV
Russia	448 459	50 417	289 800	117 646	24 355	1 919	No data (roughly less 5 000)	No data (roughly less 500)	No data

The incidences characterize present trends in the spread of HIV infections and TB disease.

the true number is somewhere between 1.5 and 2.0 million citizens, or over 2 percent of the adult population.

The epidemic is growing fastest among young people aged 15-30, the very same group that should be leading Russia into the 21st century. In December 2006, 77.9% of the total number of HIV-positive cases was registered in this age group (see Table 2). Dramatic growth of Russia’s HIV/AIDS epidemic between 1994 and 2009, as measured by official

cases of HIV and AIDS diagnosis was registered with the Russian Federal AIDS Center (see Figs. 4-6).

Although HIV infection has been reported in virtually all of Russia’s regions, there are a number of geographic “hot spots” where HIV prevalence is much higher than average. Russia’s largest urban centers, Moscow and St. Petersburg, are epicenters for HIV/AIDS. At the end of 2009, eight regions of the RF have officially registered HIV-cases higher than 20.000 cases: Irkutsk oblast, Samara oblast, Leningrad

oblast, Orenburg oblast, Sverdlovsk oblast (which includes Yekaterinburg), Moscow oblast, St. Petersburg and Moscow.

Over the past decade, HIV transmission in Russia has been concentrated within a number of high-risk populations, among which there is considerable overlap: injecting drug users, sex workers and prisoners (see Fig. 7). Men who have sex with men and migrant workers, especially those from Central Asia, are additional populations with high concentration of HIV. The future of Russia's HIV/AIDS epidemic will turn on the degree to which high risk groups serve as "bridge populations" for transmitting the virus into the heterosexual, nondrug using population. Notable indicators that this shift is already underway include the rapid rise in curable sexually transmitted infections in the general population over the last several years (see Fig. 7).

Since the early of 1990's, the drug use in Russia has exploded. There is a direct connection between injecting drug use and HIV. According to numerous studies, drug users in Russia represent a larger share of the total population when compared to other countries (see Fig. 7 and Table 3). HIV has already begun moving rapidly from this sub-culture to people who have no direct contact to drugs, often through unprotected sex.

Sex workers constitute a second important high-risk group with the potential to spread HIV into the general population. Since the collapse of the Soviet Union, sex work in Russia has increased dramatically. In Moscow, the number of professional sex workers is believed to total between 20.000 and 40.000. In St. Petersburg, the number of full-time prostitutes is estimated at 10.000.

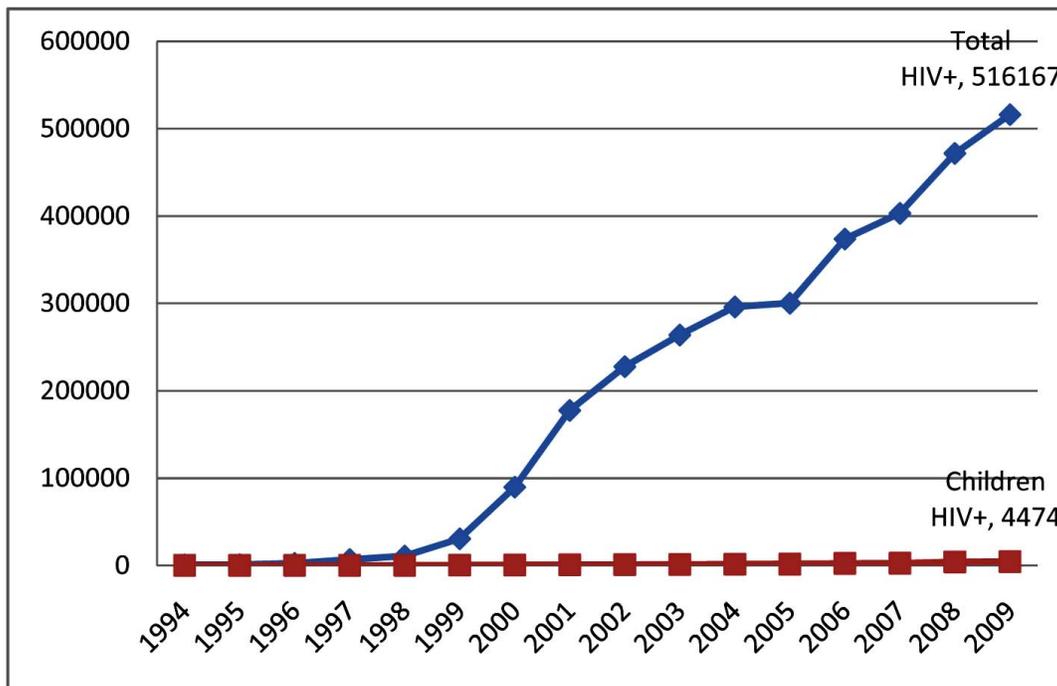


Fig. (4). Official cases of HIV diagnosis on 31 December 2009.

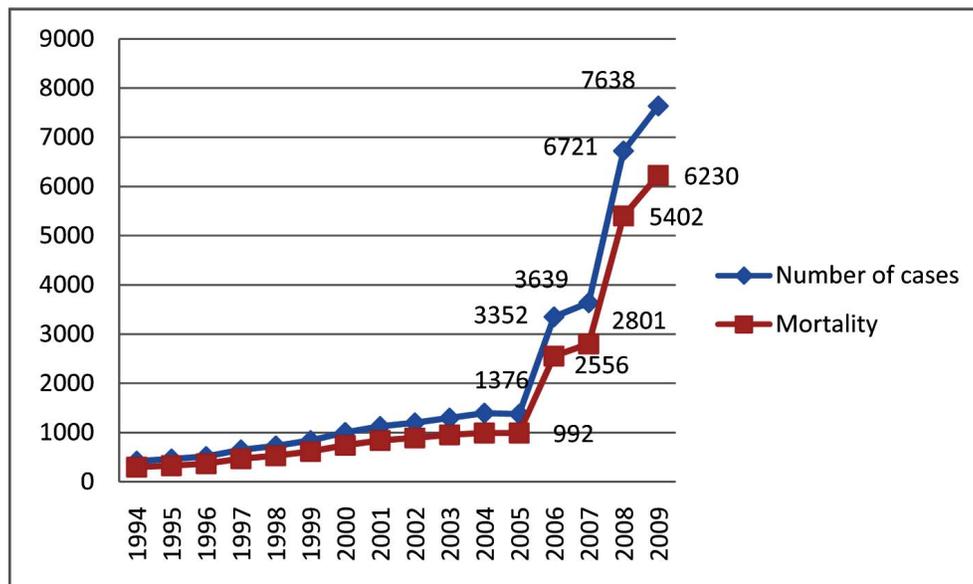


Fig. (5). The total number of AIDS diagnosis and AIDS mortality on 31 December 2009.

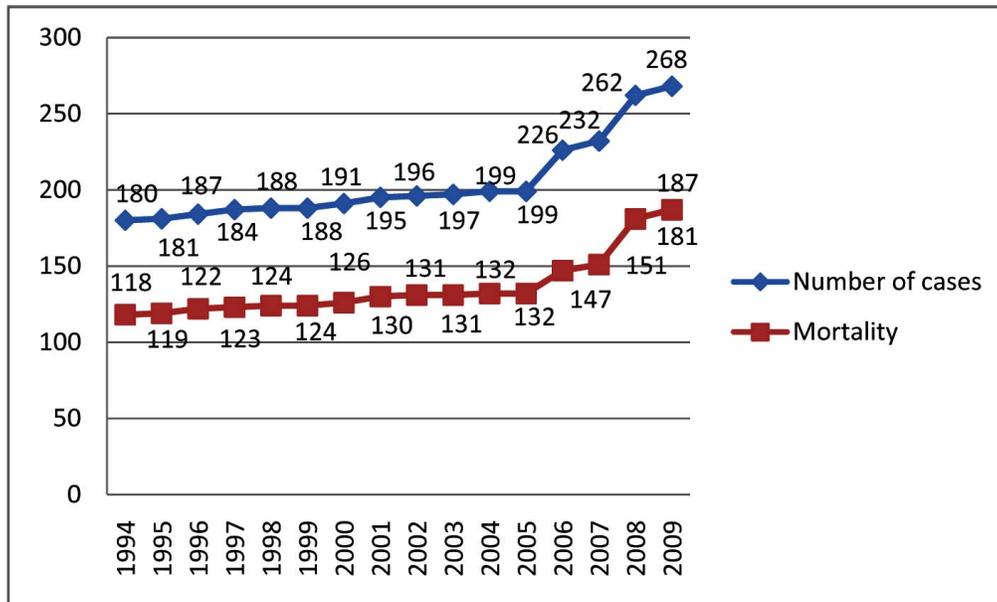


Fig. (6). The number of cases of AIDS diagnosis and AIDS mortality in children on 31 December 2009.

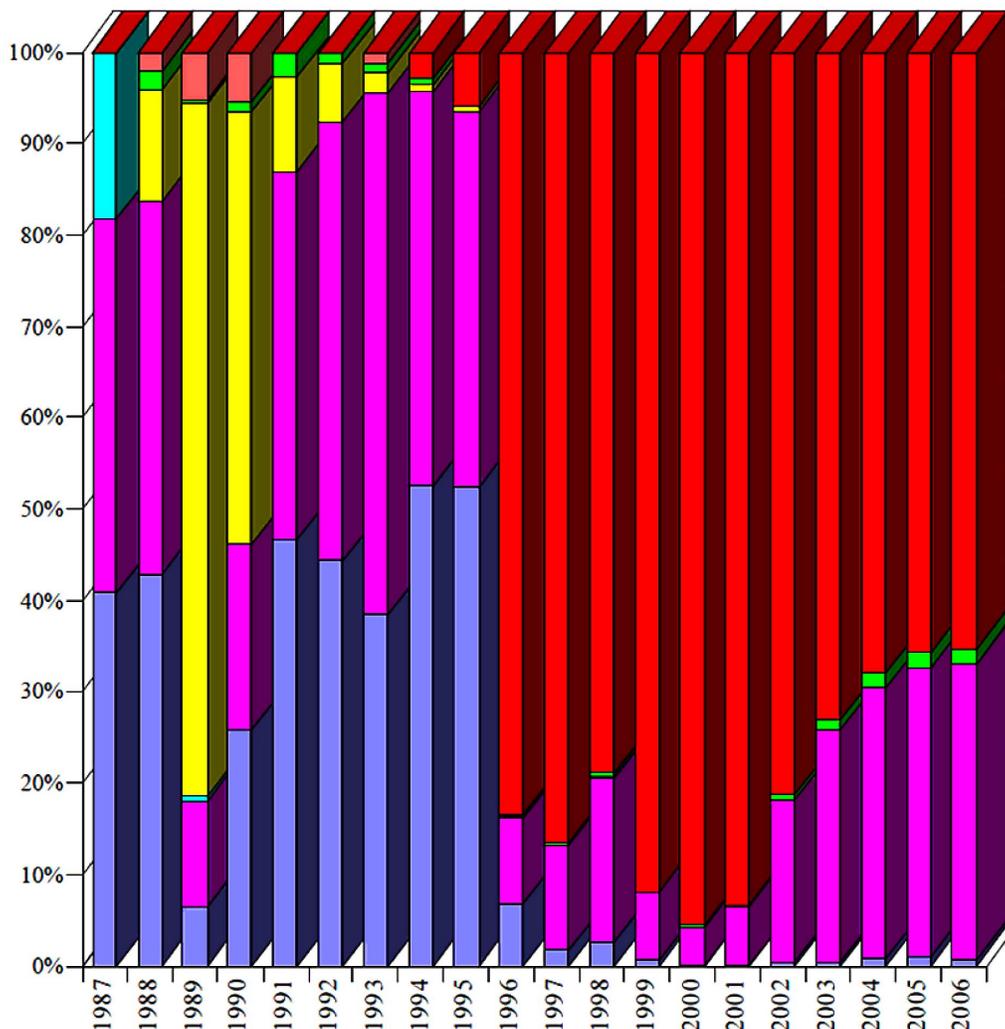


Fig. (7). HIV-positive cases distribution in RF by the core factors of infection in 1987-2006, excepting children with unstated diagnosis (% of cases). Red – Parental contact by intravenous drug injection, Pink – Infection of mothers from children at breast feeding, Green – Infection of children from HIV+ mothers during pregnancy, childbirth and breast feeding, Yellow – Staying in the nosocomial places, Blue – Decantation of the blood infected with HIV, Violet – Heterosexual contact, Grey – Homosexual contact.

Table 5. HIV-Positive and AIDS Cases Distribution in RF by Age and Gender Excepting Children with Unstated Diagnosis (on 31 December 2006)

Age	Living with HIV Infection/Died			Living with AIDS Diagnosis/Died			Total		
	Men	Women	Total	Men	Women	Total	Men	Women	Total
<1	173/6	182/9	355/15	4/7	2/6	6/15	190	199	389
1-4	456/13	440/10	896/23	27/58	30/36	57/94	554	516	1070
5-9	77/1	59/0	136/1	4/11	5/12	9/23	93	76	169
10-14	559/22	293/4	852/26	4/11	3/7	7/18	596	307	903
Children	1265/42	974/23	2239/65	39/87	40/61	79/148	1433	1098	2531
15-20	33890/1294	21295/391	55185/1685	41/139	19/76	60/215	35364	21781	57145
20-30	150391/7242	69431/1706	219822/8948	268/842	86/311	354/1153	158743	71534	230277
30-40	41359/3172	14888/742	56247/3914	157/624	38/182	195/806	45312	15850	61162
40-50	10814/1194	3982/291	14796/1485	59/247	13/56	72/303	12314	4342	46656
50-60	2414/254	1186/96	3600/350	23/62	4/15	27/77	2753	1301	4054
60-70	577/45	351/26	928/71	1/11	0/1	1/12	634	378	1012
>70	183/19	202/13	385/32	0/3	0/2	0/5	205	217	422
Adult	239628/ 13220	111335/3265	350963/16485	549/1928	160/643	709/2571	255325	115403	370728
Total	240893/13262	112309/3288	353202/16550	588/2015	200/704	788/2719	256758	116501	373259

Table 6. HIV-Positive Cases Distribution in RF in Injection Drug Users by Age and Gender (on December 2009)

Age	Living with HIV Infection/Died			Living with AIDS Diagnosis/Died			Total		
	Men	Women	Total	Men	Women	Total	Men	Women	Total
<1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
1-4	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
5-9	1/1	0/0	1/1	0/0	0/0	0/0	2	0	2
10-14	326/13	100/2	426/15	0/3	0/0	0/3	342	102	444
Children	327/14	100/2	427/16	0/3	0/0	0/3	344	102	446
15-20	20824/945	7598/239	28422/1184	29/101	9/35	38/136	21899	7881	29780
20-30	84946/5098	21123/988	106069/6086	168/536	37/156	205/692	90748	22304	113052
30-40	19537/2027	3525/364	23062/2391	66/374	6/67	72/441	22004	3962	25966
40-50	3936/672	608/92	4544/764	19/103	2/14	21/117	4730	716	5446
50-60	531/92	85/16	616/108	4/12	0/0	4/12	639	101	740
60-70	69/9	13/2	82/11	0/1	0/0	0/1	79	15	94
>70	12/0	4/2	16/2	0/0	0/0	0/0	12	6	18
Adult	129855/8843	32956/1703	162811/10546	286/1127	54/272	340/1399	140111	34985	175096
Total	130182/8857	33056/1705	163238/10562	286/1130	54/272	340/1402	140455	35087	175542

With nearly 900.000 people held in prisons and pre-detention centers, Russia has one of the world's highest ratios of inmates to total population. An estimated 1 percent of the population aged 20-64 is currently incarcerated. According to official Ministry of Justice data, as of early 2006, over 45.000 inmates in Russian prisons and pre-detention centers were HIV-positive.

Another indication that the HIV-epidemic has spread more widely into the general population is the sharp increase

in the number of babies born to women with HIV. In 2009, there were 23.268 babies born to HIV positive mothers, an increase of more than twice as comparison with 2005 and more than 30 times as against 2000 (see Tables 5 and 6).

HIV/MTB Co-Infection

According to WHO and MoH & SD RF the number of TB patients with HIV in RF is currently small, but the number is rapidly growing. Thus, TB had been diagnosed in

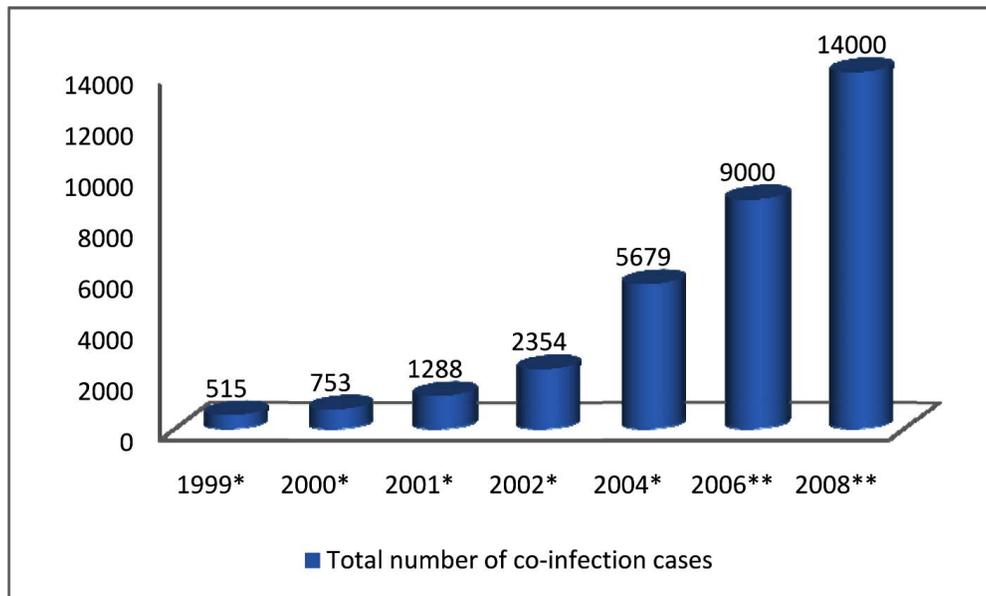


Fig. (8). The increase of HIV/MTB co-infection cases in RF. *- absolute number of cases by MoH & SD RF. **- approximate number of cases by WHO.

515 HIV-infected patients as of 1999. In 2006 this count was approximately 9.000 and in 2008 that has attained approximately 14.000 cases (see Fig. 8).

For instance, in Kaliningrad oblast, this number almost doubled in 2003 compared to 2001 (89 cases versus 48). Over 80% of these cases of TB co-infection were detected at early stages of HIV. The patients are mainly intravenous drug users (89%) and/or the homeless (68%). An analysis of patients who died of AIDS revealed that 53% had TB.

In 2004-2006 detailed research of HIV/MTB co-infection was passed on the territory of 15 regions of RF (Kalmykia Republic, Komi Republic, Tatarstan Republic, Altay kray, Krasnoyarsk kray, Kaliningrad oblast, Nizhny Novgorod oblast, Orel oblast, Perm oblast, Tambov oblast, Tula oblast, Ulianovsk oblast, Yaroslavl oblast) by Russian Federal AIDS center. In these regions, 41.470 patients with HIV infection were detected as of end of 2004, 46.014 – end of 2005, 50.766 – end of 2006. In 2004, TB was diagnosed for the first time in 382 HIV-patients, in 2005 – 535 and in 2006 – in 681 HIV patients. The steady increment of TB incidence in HIV-infected patients had registered. Per 100.000 population this indicator was 923.6 in 2004, 1162.7 – in 2005 and 1341.4 – in 2006. No less than 50% of lethal cases in HIV-infected patients at “terminal” stages of the disease (AIDS stage by the WHO criteria) have been caused by TB. The mortality increase in HIV patients by TB has been marked: 2004 – 139.9 cases per 100.000 of population, 2005 – 280.3, 2006 – 297.4 cases. The highest rates of TB incidence and mortality in HIV-infected patients have been registered in Kaliningrad oblast, Tula oblast and Ulianovsk oblast [21-23].

Given the average “lag” of six to seven years following the HIV epidemic, a sharp increase in TB incidence should be expected by next time. WHO predicts that the a third of the HIV-positives will develop TB during their lifetime and gives several reasons to this [24] :

- HIV increases the risk of MTB infection,

- HIV promotes progression to active TB in people with recently acquired and with latent MTB infection,
- Increasing TB cases in people living with HIV results in an increased risk of TB transmission to the general public,
- HIV increases risk of recurrent TB.

STATE OF THE ART IN RESEARCH

All in all about 7 000 publications on TB including HIV-associated TB were published in RF during 2000-2008. The most significant and best known are the following (in chronological order):

According to the order of MoH & SD RF 89 regions of Russia are divided into areas of supervision between 5 institutes: Central TB Research Institute of RAMS, Moscow research institute of Phthisiopulmonology named after I.M. Sechenov, Novosibirsk, Ural and St.-Petersburg TB institutes. The named above institutes function as reference centres and supervise the territories of the Russian Federation, on their basis operate the units (Centres) on drug resistant TB treatment, clinical and diagnostic departments, microbiological laboratories of the 3-rd level and the base to perform organizational and methodical work. The institutes supervise the territories, i.e. provide organizational and methodical, educational, consultative and diagnostic support through regional TB dispensaries which are responsible for all the work on TB in the region.

Besides, the “Coordination Board” and the “Centre on TB-aid to HIV-infected patients” of MoH & SD RF were set up in accordance with the “Programme of activities on TB-aid to HIV-infected patients”. In each territory operates a coordinator on HIV-associated TB, who is a member of the Board. Patients with AIDS undergo (in diagnostics centre at AIDS Center) scheduled TB examination. In his turn a phthiatrician of a TB dispensary monitors HIV-infected and patients with HIV/MTB co-infection.

The law “On TB spread prevention in RF” was passed in 2001.

The Federal programme “Urgent measures on TB control in Russia” has been performed in the Russian Federation till 2002. In 2002-2006 the Federal target program “Prophylaxis and social nature diseases control” with the subprogramme “Urgent measures on TB control in Russia” was adopted.

In 2007-2011 the Federal target programme “Prophylaxis and control of social nature diseases”, TB Component and similar target programmes in regions were adopted. Financing is realized at federal and regional levels accordingly.

EXISTING PROJECTS

In the Russian Federation in 2008 in addition to budgetary financing of TB activities some projects were realized with financial support from The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), the programme “Promoting a Strategic Response to TB Treatment and Care for Vulnerable Populations in the Russian Federation” (2005-2009). The project financing totalled 88 million US dollars.

Besides, in 2008 the GFATM project “MDR-TB diagnostics and treatment” was initiated (or approved) in 21 administrative territories of RF and in 4 Federal TB institutes.

In 2008 the World Bank project “TB and AIDS prophylaxis, diagnostics and treatment”, TB component was completed. The project financing on TB component made up 98 million US dollars.

EU Projects with Samara Region Participation

(Samara –scientific partner and subcontractor)

Genetic analysis of the host-pathogen interaction in tuberculosis: TB-EURO-GEN

Partners:

- (1) Queen Mary, University of London, Mile End Road, London E1 4NS, United Kingdom, the Coordinator
- (2) The Chancellor, Masters, and Scholars of the University of Cambridge, The Old Schools, Trinity Lane, Cambridge CB2 1TN, United Kingdom
- (3) Swedish institute for infectious disease control, Nobels Vaeg 18, Solna 17182, Sweden
- (4) Bernhard-nocht-institut fur Tropenmedizin, Bernhard Nocht Strasse 74, Hamburg 20359, Germany

A new platform for fast molecular detection of MDR and XDR resistant strains of *M. tuberculosis* and of drug resistant malaria: TM-REST

Project Co-ordinator: Dr. Daniela Cirillo (Fondazione Centro San Raffaele, Milan, Italy)

Project Partners:

- National Centre for Mycobacterial Infections, Borstel, Germany;
- University of Siena, Siena, Italy;

- National Centre for Infectious and Parasitic Diseases, Sofia, Bulgaria;
- STMicroelectronics, Catania, Italy;
- University Hospital of Lung Diseases, Tirana, Albania;
- University of Glasgow, United Kingdom
- Foundation for Innovative New Diagnostics, Geneva, Switzerland;
- Queen Mary and Westfield College, University of London
- Samara Oblast TB Service, Samara, Russian federation

Pan-European network for the study and clinical management of drug resistant tuberculosis: “TB PAN-NET”

Partners:

- FONDAZIONE CENTRO SAN RAFFAELE DEL MONTE TABOR - project coordinator
- QUEEN MARY AND WESTFIELD COLLEGE, UNIVERSITY OF LONDON
- FORSCHUNGSZENTRUM BORSTEL,
- FONDAZIONE SALVATORE MAUGERI CLINICA DEL LAVORO E DELLA RIABILITAZIONE,
- AZIENDA OSPEDALIERA SAN GERARDO DI MONZA
- EUROPEAN RESPIRATORY SOCIETY
- FOUNDATION FOR INNOVATIVE NEW DIAGNOSTICS
- SMITTSKYDDINSTITUTET,
- STATENS SERUM INSTITUT,
- HRVATSKI ZAVOD ZA JAVNO ZDRAVSTVO-
- UNIVERSITA’ DEGLI STUDI DI SIENA,
- Hain Lifescience GmbH,
- STATE AGENCY OF TUBERCULOSES AND LUNG DISEASES,
- MONTESSORI GUIDO,
- SIHTASUTUS TARTU UELIKOOLI KLIINIKUM,
- National Tuberculosis and Infectious Diseases University Hospital,
- BIOTEHNOLOGIJOS INSTITUTAS,
- NASJONALT FOLKEHELSEINSTITUTT,
- Bolnisnica Golnik Klinicni oddelek za pljucne bolezni in alergijo,
- prins leopold instituut voor tropische
- SPITALUL DE PNEUMOTIZIOLOGIE BRASOV,
- INSTITUTUL DE PNEUMOTIZIOLOGIE "MARIUS NASTA",
- INSTITUT PASTEUR DE LILLE,

- National Institute for Health and Welfare,
- INSTITUT SCIENTIFIQUE DE SANTE PUBLIQUE,
- INSTYTUT GRUZLICY I CHOROB PLUC,
- University of Medicine and Dentistry of New Jersey

a) **"TB/AIDS Control Project"** includes the following two key components: (A) "Tuberculosis" and (B) "AIDS". It will be implemented at the federal and regional levels in the health care and FPS institutions of Russia. The Project covers 86 regions of the Russian Federation. It has the following objectives: (i) to facilitate control over the epidemic spread of TB and AIDS for a short-term outlook and (ii) to stabilize and reduce these epidemic diseases' levels - for a medium-term outlook. The TB component provides for the establishment of a basis for TB high-quality diagnostics, treatment and epidemiological monitoring. It will cover at least 50% of civilian population and 100% of populations in penitentiary institutions. It is planned to additionally provide for about 3000 diagnostic laboratories of different levels. The AIDS component provides for the supply of laboratory and medical equipment to the federal and regional HIV/AIDS services (90 laboratories in the civilian sector and 10 laboratories of the penitentiary system of Russia) and STI services (20 centers). It is planned to improve epidemiological surveillance and monitoring, conduct campaigns on HIV/AIDS and STI prevention for communities and high-risk groups of population, and to provide material and technical support for 6 or 7 blood transfusion stations, to strengthen two federal consulting and diagnostic center for HIV-exposed children, including medical equipment and drugs for pregnant HIV-exposed women (2500) and newborn children (150).

b) **The National Priority Project "Health":** Carrying out of actions for preventive maintenance, revealing and treatment of some diseases (HIV-infection, hepatitis B, rubella).

Definition of a number of HIV-infected of the citizens who are subject to treatment, definition of requirement for special medicines, tests for diagnostics and the control of efficiency of treatment of HIV-infection. Carrying out of actions for prevention of expansion of HIV-infection, hepatitis B and C in the groups of the population most predisposed to infection.

DIAGNOSTIC STANDARDS

In accordance with regulating documents (orders of MoH & SD RF) the standard minimum of investigations obligatory for TB diagnosis and also a number of additional and facultative methods of examination which are performed if necessary for diagnosis specification are defined in Russia.

Obligatory standard diagnostic methods at primary health institutions, at the stage of diagnostics: clinical trial, Ziehl-Neelsen sputum smear microscopy (not less than 3 tests with quantitative estimation of SS+ (bacterioexcretion), chest X-ray, clinical blood test, Mantoux test with 2TE PPD-L at complaints of TB suspect patients or at scheduled examination (1 time annually) of the persons in risk groups.

Obligatory standard diagnostic methods in TB institutions, at the stage of diagnostics: clinical trial; Ziehl-

Neelsen sputum smear microscopy (not less than 3 tests with quantitative estimation of SS+ (bacterioexcretion), chest X-ray; and other methods of radiological diagnostics, Mantoux test with 2TE PPD-L, detection of SS+ (culture positive) on solid media; drug susceptibility testing on solid media.

Additional methods of investigation: extended microbiological diagnostics (PCR-diagnosis of sputum and fluorescence sputum smear microscopy at negative Ziehl-Neelsen microscopy); sputum inoculation on liquid media and M. tuberculosis drug susceptibility testing by BACTEC MGIT 960; M. tuberculosis drug susceptibility testing to R, H, Ft on biological microchips; PCR (polymerase chain reaction). Diagnostic standards conform to WHO diagnostic standards.

Profound (advanced) radiological diagnostics (computerized axial tomography (CAT), ultrasonic scanning and other);

Immunodiagnostics (immune-enzyme analysis H₃₇RV, TB antibodies and antigens detection, evaluation of T and B-lymphocytes quantity and functional activity and their regulatory subpopulations (helpers and suppressors), evaluation of phagocyte system functional activity, immunologic tests with chemo agents and other);

Bronchi examination (bronchoalveolar lavage, different biopsy procedures);

Other invasive methods (video thoracoscopy, pleuroscopy (thoracoscopy), mediastinoscopy, thoracotomy and other with biopsy material (tissue sampling) study with cytologic and histologic techniques);

Lungs and cardiovascular system functioning examination, biochemical investigations (liver, kidney functions, blood coagulant system, lipid peroxidation, protein metabolism, etc.)

MEDICAL TREATMENT STANDARDS

Treatment of TB patients at hospitals and at out-patient stages on the territory of RF is conducted in accordance with the orders of MoH & SD RF. Treatment of TB caused by drug sensitive *M. tuberculosis* is realized according to DOTS regimen (regimens 1, 3, 2(A)) (see Table 7).

Regimen 1 and 3

- Intensive phase - 2HRZE or 2HRZS
 - Continuation phase - 4HR or 4H3R3 or 6HE
- Therapy costs average 60 US dollars.

Regimen 2 (A)

- Intensive phase - 2HRZES + 1HRZE
 - Continuation phase - 5HRE или 5H3R3E3
- Therapy costs average 80 US dollars.

TB patients with suspected drug resistance before obtaining culture report are treated according to Regimen 2 (B).

Regimen 2 (B)

- Intensive phase - 3 HRZE +Pt +Cap(K) +Fq 3 months
- Continuation phase is defined according to culture report on drug resistance

Table 7. Average Costs for Detection of 1 TB Patient at Primary Health Care Institutions

	Average Costs Per 1 Investigation, (USD)	Number of Investigations	Number of Persons Examined to Detect 1 Patient	Average Costs Per 1 Patient Detected, (USD)
Mass fluorography examination	3	1	1000	3,000
Acid-fast <i>M. tuberculosis</i> bacilli microscopy	3	1	150	500
Tuberculin diagnostics	3	1	1	3
General blood test	6	1	1	6
Medical examination	3	2	1	6
Chest X-ray (2 projections)	35	1	1	35
Total:				3550

Annex 4a. HIV - Country Standards and Availability of Best Possible Diagnostic Tests

	Primary Diagnostics				Follow-Up		Resistance Testing	
	Screening Test	Confirmation	Viral Load Test	CD4	CD4	Viral Load	Phenotypic	Genotypic
	i.e. ELISA	i.e. Western Blot	i.e. PCR	i.e. Flow Cytometry	i.e. Flow Cytometry	i.e. PCR		
Russia	ELISA 1 - very common Immunochromatography (express test) 2 - common	1 - very common	1 - very common	3 - rare	3 - rare	1 - very common	3 - rare	2 - common

Annex 4b. MTB - Country Standards and Availability of Best Possible Diagnostic Tests

	Contact Tracing			Active Tuberculosis					Resistance Testing	
	Skin-Test	X-Ray	IGRA ("In-Tube" Gamma Interferon Release Assay)	Skin-Test	X-Ray	IGRA	AFB (Acid Fast Bacteria)	PCR	Phenotypic	Genotypic
Russia	1 - very common	1 - very common	3 - rare	1 - very common	1 - very common	3 - rare	2 - common	2 - common	2 - common	3 - rare

Treatment of patients with drug resistant TB is conducted taking into account the data on drug resistance (DOTS +) – regimen 4:

Regimen 4

- Intensive phase – at least 5 medications (drugs) preserving susceptibility (6 months) are prescribed
- Continuation phase – 18 months

Therapy costs amount to about 23 300 US dollars. In the framework of the GFATM project “MDR-TB DIAGNOSTICS AND TREATMENT” the drugs are obtained through the “Green Light” Committee (WHO). In that case therapy costs for patients with drug resistant TB can be reduced by half or three times.

Treatment of TB patients in Russia is financed by the state. Private sector does not render services in TB treatment.

	Legacy Therapy for HIV	Legacy Therapy for TB (incl MDR/XDR)
a) Country Standards and Deviation from Best Standard of Care	Treatment of HIV infection in Russia carry out on the basis of the official document: "About the statement of the standard of medical aid to people with the illness caused by a HIV at rendering of the specialised help" (the order of the Ministry of Health No 785, November, 21st, 2006). Officially applied medicines: Protease inhibitors: Amprenavir, Indinavir,	Treatment of the tuberculosis of lungs in Russia carry out on the basis of the official document: "The Principles and standards of treatment of a tuberculosis of lungs in the Russian Federation" (the order of the Ministry of Health No 109, on March, 23rd, 2003). Officially applied medicines: Intensive phase of chemotherapy: Isoniazid,

	Lopinavir, Nelfinavir, Ritonavir, Saquinavir. Reverse transcriptase inhibitors: Abacavir (ABC), Didanosine, Zalcitabine (ddC), Zidovudine (INN) or azidothymidine (AZT), Lamivudine, Nevirapine, Stavudine.	Pyrazinamide, Ethambutol, Streptomycin, Riphampicin. Phase of continuation of chemotherapy: Isoniazid, Riphampicin, Ethambutol. Strategy of treatment of a tuberculosis in Russia is close to strategy of the Alliance for the Prudent Use of Antibiotics (APUA).
b) Therapy costs (daily) for HIV / HIV-MTB co-infection/TB (incl MDR /XDR)	Therapy costs (daily) for HIV	Therapy costs (daily) for TB (incl MDR / XDR)
	\$ 0,5 mln (total expenses of the federal budget per day on HIV treatment) * \$ 1,3 (on 1 patient per day at the expense of the federal budget)	\$ 1,6-2.0 mln (total expenses of the federal budget per day on tuberculosis treatment) \$ 6-8 (on 1 patient per day at the expense of the federal budget)

* Total for 2009 year about 157 000 000 \$ to chemical therapy against HIV.

SCIENTIFIC CHALLENGES FOR THE FUTURE

No.	Project Name	Results to be Obtained
1.	Studying molecular epidemiology of <i>M. tuberculosis</i> with primary and acquired MDR and XDR in various CIS countries (Russia, Azerbaijan, Uzbekistan, Moldova, Belarus, Kazakhstan).	New and correct data on drug resistant TB prevalence rate including MDR will be obtained. Recommendations on adequate treatment regimens of patients at the initial stage of treatment with no available data on drug resistance of strains (on the average, up to 2 - 3 months), and also for SS negative patients will be developed. Recommendations to enhance National TB Programs will be prepared. Articles, reports. Implementation level - federal.
2.	Further study of molecular-biological properties of <i>M. tuberculosis</i> strains of W cluster.	The data characterizing the peculiarities of <i>M. Tuberculosis</i> strains of W cluster, reflecting possible advantages of the given cluster will be obtained. <i>M. Tuberculosis</i> belonging to W family will be characterized according to several parametres (microbiological and molecular-genetic).
3.	Working out new gene technologies for fast identification of <i>M. tuberculosis</i> and detection of their drug resistance.	New data on <i>M. tuberculosis</i> genome and mechanism of <i>M. tuberculosis</i> resistance formation to TB drugs will be obtained. New biological microchips detecting <i>M. tuberculosis</i> resistance to 1-st and 2-nd line drugs will be developed and tested. Also the masspectrometry technique to reveal <i>M. tuberculosis</i> drug resistance will be adapted.
4.	Study of TB epidemiology on the territory of the Russian Federation using molecular and genetic technologies.	Data on prevalence of <i>M. tuberculosis</i> certain strains on the territory of the Russian Federation will be obtained, channels of infection will be detected and reasons for TB outbreak will be investigated. Creation of the bank of strains and data storage.

		Adaptation of accelerated technology of polygotyping using microchip technology. Test-system to carry out accelerated polygotyping on biological microchips will be developed.
5.	Study of intracellular growth of <i>M. tuberculosis</i> strains of various genotypic clusters in <i>in vitro</i> model when infecting peritoneal macrophages of mouse.	The data characterizing the peculiarities of interaction of mycobacterium strains with cells of the host, dependence of a phenomenon on genetic- mediated expression of virulence factors will be obtained. Characteristics of growth and cytopathogenic effect of mycobacteria of various clusters phagocytied by macrophages will be studied. Estimation of expression of virulence genes and persistence of mycobacterium phagocytied by macrophages will be given. Can be used to create TB drugs with the new mechanism of action.
6.	The role and study of surfactant system in pathogenesis of pulmonary TB.	Evaluation of state of pulmonary surfactant and alveolar macrophages under sharp pulmonary TB progression will be given. Effect of various combinations of TB drugs on surfactant production by alveolocyttes of the 2nd type will be studied. Possibility of activation of surfactant system of the lung changed as a result of TB by pharmacological drugs and exogenous surfactant will be studied.
7.	Molecular-genetic investigations of genes determining hereditary predisposition to mycobacterial diseases	The genetic markers determining predisposition to TB will be detected. Our knowledge on functioning of the general immune mechanisms of stability to mycobacterial pathogen will be expanded. Computer databank and bank of DNA samples from patients and healthy people will be generated. Computer databank and bank of DNA samples from patients and healthy people will be supplemented. Probable models of genetic stability to TB will be developed, general genetic markers of the studied genes for TB and leprosy sensitivity will be detected. Setting up of genetic consultation centre regarding predisposition to mycobacterial diseases.
8.	Studying the impact of the genes of chromosome 6 of a man on sensitivity to tuberculosis	The genetic markers determining predisposition to TB will be detected. Our knowledge on functioning of the general immune mechanisms of stability to mycobacterial pathogen will be expanded and mutations of genes determining susceptibility to TB will be detected. Complexes of genetic markers according to HLA system and genes PARK2 and PACRG including extensive haplotypes and genotypic combinations in connection with sensitivity to TB will be studied. Setting up of genetic consultation centre regarding predisposition to mycobacterial diseases. Articles, reports
9.	IgG response in pulmonary TB patients: subclass studies.	The goal of this study is evaluation of IgG antibodies belonging to distant subclasses in pulmonary TB patients in order to establish their possible roles in TB course.

		Anticipated results of the IgG isotypes' studying will be superposed dynamically against the observed clinical TB symptoms and the efficacy of drug treatment. Development of the IgG isotypic responses against individual mycobacterial antigens will be evaluated with regard to the parallel shifts in the expression of differentiation factors involved in the CD4 ⁺ cells development, as well as production of several cytokines. We also plan to evaluate isotype-specific local IgG responses in the lung tissue. As a practical aspect, we plan to create new preparations of anti-human IgG isotype-specific monoclonal antibodies potentially useful for TB serodiagnosis.
10.	Establishment of specific molecular vectors useful for transportation of anti-TB drugs towards TB foci.	The goal of this study is to create on the basis of anti-TB monoclonal antibodies (mAbs) molecular tools able to carry drugs towards TB foci. The established assembled preparations will be studied with regard to their efficacy against mycobacteria <i>in vitro</i> and <i>in vivo</i> . We plan to develop mAbs specific for the protease and glycosidase-resistant surface mycobacterial antigens. These mAbs will be conjugated with anti-TB drugs. The object of the study: intracellular anti-TB therapy. Practical aspect: development of new tools delivering drugs into TB foci.

Major Research Topics	Remarks
1. Experimental revision of approaches to creation of a vaccine against HIV on the basis of different mechanisms of the virus penetration.	There is a proved opinion that dynamics of a HIV infection and genetic transformation of a virus in the individual is essentially various at sexual contact (mucous membrane) and at injection (the heroin use).
2. Designing of the virus killing HIV infected cells.	The ineffectual history of creation of a vaccine against a HIV has more than 10 years. There is no working vaccine against retroviruses. It is necessary to turn researches on 180 degrees.
3. Search or designing of the substances (molecules) killing a HIV infected cells.	
4. The expanded clinical trials of the Interleukin 1 beta for radical treatment of a tuberculosis, Hepatitis B and C, and, probably, HIV infection	The interleukin 1 beta in Russia is an official intravenous medicine within more than 10 years. The limited clinical trials for treatment of hepatitis B and C, and also a herpes and a tuberculosis have shown fantastic results. Full treatment for hepatitis B and C about 70 % and a tuberculosis more than 90 %, including in cases MDR and XDR. For treatment of an infection of a HIV the Interleukin 1 beta did not study.
5. Development and clinical trials of a vaccine against heroin.	In Russia the main social group subject to HIV infection, hepatitis and tuberculosis are heroin addicts (more than 60%).
6. Development of the confirming test of new generation for a HIV infection and an active phase of a tuberculosis without use of devices and laboratories (the "field" test).	In Russia exists advancing technologies for creation of such test on the basis of magnetic nanoparticles and a chromatography in a thin layer. Money resources are necessary for completion of this technology.

7. Realisation of real statistical researches in the closed groups of addicts concerning contamination of a HIV and a tuberculosis.	Now there are no real statistical data and consequently there is no practicable plan of work with this group.
8. Search of plant and other natural new classes of substances for effective treatment of the tuberculosis	Dynamics of occurrence of new strains steady against antibiotics shows, that treatment of a tuberculosis by means of antibiotics will be successful no more than 5-10 years. New antibiotics are more and more toxic for people.
9. Designing of essentially new tubercular mucosal vaccine alternative to BCG.	BCG vaccine has no 100% efficiency as does not protect from primary colonisation of bacteria on a mucous membrane.
10. Studying of the prostitutes having long experience in critical areas, but not infected with HIV.	It is necessary to receive authentic data on existence of genetic or not genetic natural resistibility to a HIV.

EXISTING FUNDING PROGRAMMES

TB Activities Budget in RF in 2008

	Budget/USD	Deficit /USD
DOTS	384 millions	0,8 millions
Treatment of patients with MDR (including HIV/MTB co-infection)	269 millions	112 millions
Other costs	69 millions	13,7 millions

National (and Bilateral) Funding Programs

Mechanisms of inhibition of viral replication by plant polyphenols [26]	Russian Foundation for Basic Research
Development of methods of complex laboratory researches of applicant (potential, challenging, prospective, promising) vaccines against HIV/AIDS on the basis of recombinant proteins [25, 28]	The State Research Centre of Russian Federation "Institute of Immunology"
Studying of a HIV circulation in the Euroasian territory and creation of the atlas on the basis of the received information	The Ministry of Health of the Russian Federation

Global Funding Programs

Sixth Research and Technological Development Framework Programme of the European Commission: European Vaccines and Microbicides Enterprise [27-30]	European Commission
Global HIV/AIDS Vaccine Enterprise - Consortium on Global HIV vaccine Research Cryorepository - GHRC	Global HIV/AIDS Vaccine Enterprise The Bill & Melinda Gates Foundation

INTERCULTURAL SENSITIVITIES

The unified system of TB activities (TB and TB/HIV prophylaxis, detection, diagnostics and treatment) and unified reporting and accounting documentation which are regulated by the orders of MoH & SD RF are adopted in the Russian Federation.

National features of mentality of various ethnic nationalities living in the Russian Federation can become apparent only in their relation to these activities.

Intercultural differences and sensitivities	Intercultural differences and sensitivities in Russia are insignificant. At least in the field of public health services.
Site specific policies	Officially usual European policies take place. Practically a considerable arbitrariness of officials and corruption takes place.
Sample volumes	Free of charge to 20 ml of blood With payment - to 400ml
Ethical approval/level of ethical regulation	Usual European level
Operational challenges such as electricity, transport, internet connectivity, etc	The electricity, transport, internet connectivity without especial problems
Language barriers	Language barriers in Russia do not exist

CONCLUSION AND REFLECTIONS

The first years of the 21st century are characterized in the Russian Federation by certain stabilization of the basic epidemiological TB rates and indicators showing efficiency of TB activities. At the same time the situation remains serious enough.

Numerous factors affecting TB dissemination demand thorough study. The problem of HIV-associated TB is of great importance to Russia.

Prevalence growth of associated infection can cause serious damage to population health of the country when appropriate activities are not carried out.

In order to enhance monitoring of HIV-associated TB it is essential to introduce everywhere a uniform system of registration of cases with associated infection.

Thus, TB situation in the Russian Federation is complicated enough and the necessity to further enhance TB control performance and implement modern methods to stop the disease prevails.

Development and implementation of new diagnostic and medical technologies offer major challenge. To achieve this, thorough support of scientific research activities and projects is vital. Here, it is important to rely on both wide experience of the Russian phthisiology and international experience, including the neighbouring European countries.

CONCLUSION

TB plays significant role in pathogenesis HIV as opportune infection and concomitant diseases. In 2004 in analytical review scientists predicted significant worsening

of epidemic situation in Russia at next years because of developing HIV into AIDS, and accordingly to prediction more than half of HIV-infected with AIDS will suffer TB. Scientists of Federal scientific-methodology center of preventing of AIDS conducted researching from 2004 to 2006. They showed that in 15 regions of Russian Federation not less than in 50% cases death reason of HIV-infected was TB. These data shows pathogenic correlation between TB and HIV.

There are two periods in developing of prevalence of TB in Russia. There is period of violent growth from 1992 to 2000 when number of TB-infected increased in 2,5 times (about 16,9% in year). This growth was caused by worsening of social factors and insufficient financing of anti-TB measures. Spreading of HIV promoted spreading of TB infection, especially among injection drug addicts. Next period was from 2001 to 2004. There was slowing down of spreading infection but was spreading of different TB forms. At present there are about 290 000 TB infected in Russia.

There is evident correlation between TB and AIDS. Results of investigations in number of developing countries shows that about 70% TB-infected have HIV. More over, about 50% HIV-infected have high risk to get developing of TB in view weakening of immune system. TB is being the main accompanier of AIDS among more than half of all HIV-infected in developing countries where live about 95% per cent of all HIV-infected. In industrial countries there is observing signs of revival TB because of spreading AIDS.

REFLECTIONS

TB is one of the main death reasons of HIV-infected. The more per cent of HIV-infected in country, the more level of deaths from TB.

There is problem of early diagnostic of TB and AIDS. TB-infected patients have high per cent of destructed lung tissue and being source of infection for long. Among first diagnosed TB-infected there is low virus load and some diagnostic systems are not sensitive to them. Also one of the main problem is high genetic variability of HIV and multi-drug resistant of HIV and MTB.

Strengthening international collaboration on therapies, a cure, and a vaccine and mobilizing world resources, scientists and international organizations in the fight against AIDS will help in struggle against AIDS and TB.

About 13 million people in the world are being carries of HIV and MTB at the same time. TB like usual catarrhal disease transmits airily. Struggle against AIDS/TB is the problem of world health and world society.

The cumulative number of the registered citizens with HIV infection is 448 thousand. Number of the citizens infected with MTB is about 290 thousand. At first sight it is not a catastrophic picture. However, the situation in Russia sharply differs from a situation in other countries. Contamination with HIV among the registered addicts is 74%. Their approximate quantity is 400 thousand. The quantity of not registered consumers of heavy drugs is 3 times more. Contamination with MTB among not registered addicts is extremely high and they do not visit medical institutions. Our estimation of quantity of addicts of

simultaneously infected with HIV and MTB makes from 20 to 100 thousand. The problem is extremely serious.

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ABBREVIATIONS

AIDS	=	Acquired immunodeficiency syndrome
ART	=	Antiretroviral therapy
DOTS	=	Directly observed therapy-short course
GFATM	=	Global Fund to Fight AIDS, Tuberculosis and Malaria
HIV	=	Human immunodeficiency virus
IRIS	=	Immune reconstitution inflammatory syndrome
MDR	=	Multidrug resistant
MTB	=	<i>M. tuberculosis</i>
PCR	=	Polymerase chain reaction
TB	=	Tuberculosis
WHO	=	World Health Organisation
XDR	=	Extensively drug resistant

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