Global Fund Against TB, Malaria and AIDS

Main Medical Department of Ministry of Justice of Azerbaijan Republic

Public Health and Reforms Center Ministry of Health of Azerbaijan Republic

OPERATIONAL RESEARCH ON "IMPACT OF HIV AND HEPATITIS C CO-INFECTIONS ON RESULTS OF MDR-TB TREATMENT AMONG PRISONERS"

REPORT

(28 March 2011 - 28 March 2013)

– Baku, 2013 –

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Acknowledgment

This study has been conducted in favor of well-coordinated work of various specialists.

We would like to express our gratitude to the Global Fund, , to all participant from Main Medical Department and PIU of Ministry of Justice.

Our great respect is to Dr. Alexandr Pasechnikov, who shared his knowledge with us with great pleasure.

Unfortunately, we can’t thank Farida Mammadyarova for valuable input in our study due to sudden death.

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Abbreviations

AIDS – Acquired Immunodeficiency Syndrome
ALT – Alanine Aminotransferase
AMK – Amikacin
AST – Aspartate Aminotransferase
ART – Antiretroviral Therapy
BMI – Body-mass index
CDC – Center of Disease Control
CPM – Capreomycin
DOTS – Directly Observed Treatment, Short-course.
DRS – Drug Resistance Survey
HBV – Hepatitis B virus
HBsAg – Superficial antigen of hepatitis B virus
HCV – Hepatitis C virus
HIV – Human immunodeficiency virus
INH – Isoniazid
KM – Kanamycin
MDR – Multi Drug Resistant
MDR-TB – Multidrug**-**resistant tuberculosis
MOJ – Ministry of Justice
MOH – Ministry of Health
NTP – National Tuberculosis Program
PWID – People who inject drugs
RMP – Rifampicin
TB – Tuberculosis
XDR-TB – Extensively drug-resistant tuberculosis
WHO – World Health Organization

Project activities

Study of risk factors existed in prison and their impact on MDR-TB treatment outcomes, and also elaborating preventive measures to eliminate them may be resulted in declining the distribution of TB in society.

The study steps included elaborating proper methodological issue, literature review, statistical and comparative analysis and presenting results. The project headed by coordinator Rauf Mammadov divided responsibilities between the following participants: A.Pasechnikov as a TB advisor («Abt Associates İnc."), Asker İsmaylov (the executive director of PIU of 9th Round Global Fund"s TB), staff of Main Medical Office of MOJ- Fuzuli Huseynov, Naila Karimova, Rasim Tahirli. They defined the purpose of future Operational Research, theoretical and practical significance of its expected outcomes, its timeframe and job division between participants on various stage of research, and outlined operational research as follow:

- Dividing studying cohorts into two groups of patients with success and failure of treatment outcomes.
- Choosing the expected risk factors and revealing their association with MDR-TB treatment outcomes by means of univariate analysis.
- Selecting risk factors associated with MDR-TB failure and conducting their analysis by multivariate logistic regression analysis.
- Making final conclusion and recommendation of operational research based on statistic analysis outcomes.

Summary

Background: Tuberculosis (TB) is one of the world's deadliest diseases. TB has never spread as today do. Population size growth and other factors, particularly HIV, contribute to TB incidence. Multidrug**-**resistant tuberculosis **(**MDR-TB) defined as Mycobacterium tuberculosis resistant to at least isoniazid (INH) and rifampicin (RMP) (the two most powerful anti-TB drugs), is a rapidly emerging disease characterized by difficulties in treatment (longer, more expensive and with toxic drugs) and high rates of morbidity and mortality.

Although many countries have increased efforts to provide MDR-TB treatment, the recent global emergence of extensively drug-resistant tuberculosis (XDR-TB, defined as MDR-TB with resistance to a fluoroquinolone and either kanamycin (KM), amikacin (AMK) or capreomycin (CPM) has highlighted the possibility that it may be worse to provide inadequate treatment for MDR-TB than to provide no treatment at all.

In some low-incidence countries however, there was a higher risk of TB in prisons than in the general population. This was related to the higher rate of TB transmission there due to poor control measures and/or the concentration of vulnerable population sub-groups.

Some co-infection associated with MDR-TB outcome, but still not clear to what extent. It impacts on MDR-TB treatment. This fact reasoned us to investigate the role of co-infection HIV, HBV and HCV in MDR-TB treatment in prison.

Context: According to the data from MOJ the prevalence of hepatitis infection is very high among the prisoners and growths up to 60%. The importance of the research has been determined by the lack of knowledge about the role of co-infection and other risk factors in MDR-TB treatment, particularly in prison, where the prevalence rate of HIV and hepatitis C&B co-infection was higher than among the general population due to some social, environmental features of detainers life[1]. However, the information about impact of co-infection alone and in cooperation with other risk factors on MDR-TB treatment outcome is limited.

Objective: The aim of operational research is to analyze the poor results of treatment of MDR-TB and define risk factors.

Materials and methods: The analysis is based on literature review, univariate and multivariate logistic regression analysis. The study covered prisoners with MDR-TB and hepatitis B&C (seropositive) and HIV co-infection, who had their treatment with

[1] Liviana Calzavara PhD, Nancy Ramuscak MSc, Ann N. Burchell MSc Carol Swantee BSc,Ted Myers PhD, Peter Ford MD, Margaret Fearon MB, Sue Raymond RN Prevalence of HIV and hepatitis C virus infections among inmates of Ontario remand facilities .CMAJ July 31, 2007 vol. 177 no. 3 257-261

second line medicines during April 28th 2007 and December 16th 2010 year (289 cases), out of which 75.8% (219) – cured, 17% (49)-died or failure, 7.2% (21) - non-completed (defaulted or transfer out). Analyzing risk factors we focused on 268 patients that completed treatment as Inclusion criteria.

Examination of blood for antibodies to hepatitis B and C co-infection revealed that 66.2% of patients were seropositive, among which 4.4% person had hepatitis B co-infection, while 90.7% patients had hepatitis C co-infection, and just 4.9% had combination of both co-infections. In contrary, HIV|AIDS was revealed in just 5.5% (16) of patients with MDR-TB, half of which received ARV therapy.

Appointment of chemotherapy regimen, as well as monitoring and evaluation of treatment outcomes for all patients was carried out on the basis on information about susceptibility to the drugs of the first and second line, previous treatment, and it was made in strict accordance with international standards on treatment of MDR-TB patients, adopted by WHO.[2]

We analyzed all available risk factors, including severity degree markers.

Results: Out of 268 patients completed treatment with second line medicine 18.3% (49) had poor outcome (treatment failure or dead), while 81.7% (219) of patients had success.

Factors associated with treatment outcome. The univariate statistical analysis of risk factors for treatment failure in patients with MDR-TB identified several variables significantly ($p<0.05$) associated with poor treatment outcome, those are: total number of imprisonment, contact with MDR patients, diabetes mellitus, low BMI at start of treatment, existence of cavities in both lungs, lack of smear and culture conversion on 2nd month of treatment , resistance to Ofx, disease severity markers 10 and more than 10 points, side effects of 1st and 2nd line drugs such as hearing loss and hypomagnesaemia.

We did not conduct qualitative analysis in terms of HIV due to its low prevalence among our study population.

In contrary, we had high prevalence of hepatitis among our patients with MDR-TB, however, in our research any association between hepatitis and MDR-TB treatment failure has not been revealed (p=0.590).

[2]Treatment of tuberculosis. Guidelines, Fourth edition, World Health Organization 2010, Geneva

Multivariate logistic regression revealed two risk factors, predicting MDR-TB treatment outcome, such as cavity in both lungs and positive culture result at the second month of treatment.

According to multivariate logistic regression outcomes, bilateral destruction in lungs had OR=0.1 (95% CI 0.01-0.85) and positive sputum culture result (SS+/C+)at the second month with OR =0,17 (95% CI 0.06-0.54). Thus, multivariate analysis confirmed the importance of delaying sputum conversion in the second month of treatmentand cavities in both lungs that as prognostic signs - independent predictors of treatment failure.

Conclusion: We conducted study to reveal impact of HBV, HCV and HIV co-infections on treatment outcome of MDR-TB patients in prison.

The data analysis did not give markedly proof of the influence of HBV, HBC –co-infections on MDR-TB poor outcomes.

The role of HIV in MDR-TB treatment outcome remained unclear due to low prevalence HIV among prisoners with MDR-TB in prisons in Azerbaijan.

Nevertheless, the univariate analysis of data revealed risk factors, such as frequency of imprisonment less than three time, contact with MDR-TB patients, diabetes, low BMI, cavity in both lungs, positive sputum smear and culture results at the first and second month of treatment, resistance to Ofx, hearing loss, hypomagnesaemia, disease severity markers.

Multivariate logistic regression assigned cavities in both lungs and positive culture result at the second month of treatment as predictors of failure of MDR-TB treatment in penitentiary system.

1. Introduction

1.1 Tuberculosis as a worldwide public health threat

TB is one of the world's deadliest diseases. TB has never spread as today do. Population size growth and other medical and non-medical factors, particularly HIV, contribute to TB incidence. The following data from CDC Agency of the USA embodied TB as public health problem, requiring immediate and continuous interventions: one third of the world's population is infected with TB; nearly 9 million people around the world become sick with TB and almost 2 million TB-related deaths worldwide are registered annually; TB is the leading killer of people who are HIV infected. Thus, TB is one of the main problems of world health system.[3]

Recommended by WHO Stop TB Strategy, has been launched in 2006.Despite of worldwide efforts in reducing TB, the global burden of TB remains enormous. Last estimation revealed, that there were an estimated 8.7 million incident cases of TB in 2011 (13% co-infected with HIV), 1.4 million deaths from TB (990 000 deaths among HIV-negative individuals and 430 000 among people who were HIV-positive). These deaths included 0.5 million among women, making TB one of the top killers of women worldwide.[4]

The situation is still dramatic despite the availability of short-course regimens of first-line drugs since the 1980s that can cure around 90% of cases.[5]

Despite of partially achievement in 2011 of the 2015 Millennium Development Goals (MDG) target of halting the prevalence and death associated with TB and reversing its incidence, the prevalence of TB and TB mortality were still high. It will therefore not be possible to reach the target of 50% reduction by 2015.[6]

TB is an infectious disease caused by the bacillus *Mycobacterium tuberculosis*. It typically affects the lungs (pulmonary TB), but can also affect other sites as well (extrapulmonary TB). The probability of developing TB is much higher among people with decreased immune system response, such as the HIV infected persons. TB is more common among men than women, and affects mostly adults in the economically productive age groups. Overall, there were twice as many male cases reported as female cases, however a large variation was observed for male predominance in the gender distribution of TB cases[7]. In 2011, most of the new TB cases registered were in

[3]THE GLOBAL PLAN TO STOP TB 2011–2015.Transforming the fight.Towards elimination of tuberculosis.WHO. 2010.
[4]Global tuberculosis report 2012, WHO, Geneva
[5]Global tuberculosis report 2012, WHO, Geneva
[6]SURVEILLANCE REPORT.Tuberculosis surveillance and monitoring in Europe 2013, WHO/Europe and ECDC
[7] SURVEILLANCE REPORT.Tuberculosis surveillance and monitoring in Europe 2013, WHO/Europe and ECDC

the 25–44 years age group (41%). Over the last five years, region-wide trends in overall TB notification among children (age group 0–14 years) have decreased by 23%. However, the average percentage of patients within this age group has remained stable at around 6% over the same period.[8]

Without treatment, mortality rates of TB are high. In studies of the natural history of the disease among sputum smear-positive and HIV-negative cases of pulmonary TB, it was revealed that around 70% of them died within 10 years; among culture-positive (but smear-negative) cases20% died within 10 years[9]. İn Europe in 2011 71% out of all types and forms of TB, were identified as new cases, of those 55% were confirmed by sputum smear microscopy and/ or culture. It means that almost one third of all registered cases were previously treated ones/

The most common method for diagnosing TB worldwide is sputum smear microscopy. In countries with more developed laboratory capacity, cases of TB are also diagnosed via culture methods (the current reference standard).

Treatment of new drug-susceptible TB cases consists of a 6-month regimen of four first-line drugs: isoniazid, rifampicin, ethambutol and pyrazinamide.

Trying to cope with global emerging TB as public health problem WHO developed DOTS strategy, a five-component package comprising political commitment, diagnosis by means of sputum smear microscopy, a regular supply of first-line anti-TB drugs, short-course chemotherapy and a standard system for recording and reporting the number of cases detected by national TB control programmes (NTPs) and the outcomes of treatment.

1.2. Hepatitis B&C and HIV co-infection in patients with TB

The emergence of active actions against TB is stipulated by that some health conditions favoring to catch TB as well as impact on TB treatment outcome. From above mentioned TB world statistics it is obvious, that If TB is not stopped the future distribution of TB would be enormous. The *Tables 1* and *2* shows the estimated number of people living with HIV, TB, HCV, HBV in the world and in Europe

Table 1: Estimated population with HIV, HCV, HBV, TB in the world

HİV	33.4 mln.
TB	11.1 mln.
MDR TB	440 thsd.
HBV	350 mln.
HCV	180 mln.

[8]SURVEILLANCE REPORT.Tuberculosis surveillance and monitoring in Europe 2013, WHO/Europe and ECDC
[9]SURVEILLANCE REPORT.Tuberculosis surveillance and monitoring in Europe 2013, WHO/Europe and ECDC

HİV/TB*	1.4 mln.
HİV/HBV	2-4 mln.
HİV/HCV	4-5 mln.

*Number of TB cases among HIV-pozitiv people

Table 2: Estimated population with HIV, HCV, HBV, TB in Europe

HIV	2.3 mln.
TB	0.4 mln.
MDR-TB	81 thsd
HBV	18 mln.
HCV	5-10 mln.
HİV/TB*	25 thsd
HİV/HBV	0.15-0.25 mln.
HİV/HCV	0.5-1 mln.

* Number of TB cases among HIV-pozitiv people
Sourse: WHO 2009; 2010. UNAIDS 2009

1.2.1 TB/HIV coinfection

TB is the most prevalent cause of illness and mortality in people living with HIV/AIDS, and few countries address TB/HIV coinfection in a comprehensive manner [10].

People living with TB/HIV coinfection should get 6 months preventive treatment with izoniazid due to high risk of developing active TB. among their. However, resistant to izoniazid increases probability of emerging disease [11].

Thus, TB is one of the main and wide-spread disease among all other that are indicators for IIV/AIDS. Sometimes, the proportion of developing active TB among the people living with HIV/AIDS may increase up to 49 % [12].

1.2.1.1 Initiating ART for patients living with HIV/AIDS and active form of TB.

HIV infection significantly increases the risk of progression from latent to active TB disease. The CD4 cell count influences both the frequency and severity of active TB disease. Active TB also negatively affects HIV disease. It may be associated with a higher HIV viral load and more rapid progression of HIV disease.

Recently clinical trials are complementary in defining the need for ART and use of CD4 count and clinical status to inform decisions on the optimal time to initiate ART in

[10] The Berlin Declaration on Tuberculosis, WHO, 2007
[11] Apvienība HIV.LV 2010. Gada aprīlis ТБ и коинфекция ТБ/ВИЧ в Латвии Краткий обзор ситуации. http://tbpolicy.ru/publications/?id=301
[12] Apvienība HIV.LV 2010. Gada aprīlis ТБ и коинфекция ТБ/ВИЧ в Латвии Краткий обзор ситуации. http://tbpolicy.ru/publications/?id=301

patients with HIV and TB disease. Earlier initiation of ART within 2 to 4 weeks of TB treatment should be strongly considered for patients with CD4 cell counts from 50 to 200 cells/mm^3 who have evidence of clinical disease of major severity as indicated by clinical evaluation, low Karnofsky score, low BMI, low hemoglobin, low albumin, or organ system dysfunction (BI). Initiation of ART within 2 to 4 weeks also should be considered for patients with CD4 counts >200 cells/mm^3 who present with evidence of severe disease (BIII) [13] [14].

Mortality rates in patients with MDR or XDR TB and HIV coinfection are very high. Retrospective case control studies and case series provide growing evidence of better outcomes associated with receipt of ART in such coinfected patients,[15] but the optimal timing for initiation of ART is unknown.

According to latest recomendation of WHO , in patients with active TB ART should be initiated regardless CD 4 count [16].

It was revealed that among the people living with HIV/AIDS the TB treatment outcomes distributed as following :the proportion of cured person less than 50%, proportion of default cases 4 times and death 6 times more than in people without HIV/AIDS[17].

People living with HIV/AIDS should be screened for TB during every visit to doctor due to high risk of getting TB. *Vice versa*, people living with TB should be examined for HIV/AIDS. To avoid the activation of TB people infected with HIV should intake monotherapy with izoniazid as preventive measure .In addition, co-trimoxazol is prescribed for all TB/HIV cases [18].

Ideally, HIV-infected patients with high suceptibility to diseases should be placed separately from other patients in clinics, unfortunately, majority of hospitals don't have effective infection control measures.

Recently, the number of people with HIV and TB has tendency to increase.For example, the large epidemic outbreak of HIV among the European and Asian countries was defined in Ukraine in 2009 , that affected 350 000 people and 1.1% of older population. Moreover, similarity of risk factors of HIV and TB increases the emerging of

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[13] Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. http://aidsinfo.nih.gov/guidelines Developed by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

[14] Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. N Engl J Med. Oct 20 2011;365(16):1492-1501.

[15] Dheda K, Shean K, Zumla A, et al. Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. Lancet. May 22 2010;375(9728):1798-1807.

[16] Patient evaluation and antiretroviral treatment for adults and adolescents. Clinical Protocol for the WHO European Region (2012 revision), WHO, Copenhagen, Denmark

[17] Biedrība Apvienība HIV.LV 2010. *Gada aprīlis* ТБ и коинфекция ТБ/ВИЧ в Латвии Краткий обзор ситуации. http://tbpolicy.ru/publications/?id=301

[18] Pierpaolo de Colombani and Jaap Veen Review of the National Tuberculosis Programme in Ukraine .WHO, October 2010

coinfections and scale up the dramatic statistics. E.g., in 2008 in Ukraine 48 % of all death (2792) among people with HIV/TB coinfection was caused by TB [19].

1.2.2 TB/hepatitis coinfection.

Length, effectiveness of and adherence to TB treatment can also be defined by the status of liver functions.

Increasing aminotransferases by any reasons during TB treatment is described as an important risk factor for emerging hepatic toxic changes [20].

1.2.2.1 TB/ chronic HBV coinfection

Existence of chronic HBV infection doesn't negatively affect on effectiveness monotherapy with izoniazid among young people [21]. In contrary, treatment regimen with several antiTB drugs raises the risk of toxic changes of liver, fulminant hepatic falure. Such conditions can be observed even among the patient who before TB treatment has normal aminortansferase level and no histologic changing , and Hbe Ag. It is known that in patient with HBV infection anti TB treatment speeds up virus replication resulting in raising HBV-DNA and clinic manifestation of hepatitis [22].

To avoid above mentioned liver problems patients with HBV infection should get specific treatment for hepatitis before or together with TB treatment [23].

1.2.2.2 TB / Chronic HCV infection

As in the case with HBV, existence of chronic HCV infection doesn't raise the risk of emerging the hepatic toxic problems during the monotherapy with izoniazid [24]. However, applying treatment regimen with several medicines increases this risk 5 times, and additonal HIV infection raises the risk up to 14 times [25] [26]. Initiating antiviral

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[19]. A retrospective assessment of HIV mortality in 2008 in 10 *oblasts* of Ukraine (Dnepropetrovsk, Donetsk, Volynsk-Lutsk, Sumy, Zhytomir, Kharkiv and Kherson *oblasts*, the Autonomous Republic of Crimea, Kyiv City and Odessa City) . Ukrainian AIDS Centre WHO report 2010, page 14

[20] *Bahaa E. Senousy, Sanaa I. Belal and Peter V. Draganov* (Senousy, B. E. *et al.* Hepatotoxic effects of therapies for tuberculosis. Review/ *Nat. Rev. Gastroenterol. Hepatol.* 7, 543–556 (2010).

[21] McGlynn, K. A., Lustbader, E. D., Sharrar, R. G., Murphy, E. C. & London, W. T. Isoniazid prophylaxis in hepatitis B carriers. *Am. Rev. Respir. Dis.* 134, 666–668 (1986).tuberculosis. *Am. Rev. Respir. Dis.* 118, 461–466 (1978).

[22] Wu, J. C. *et al.* Isoniazid-rifampin-induced hepatitis in hepatitis B carriers. *Gastroenterology* 98, 502–504 (1990).

[23] Yu, W. C. *et al.* Lamivudine enabled isoniazid and rifampicin treatment in pulmonary tuberculosis and hepatitis B co-infection. *Int. J.Tuberc. Lung Dis.* 10, 824–825 (2006

[24] Verma, S. & Kaplowitz, N. in *Drug-Induced Liver Disease* 2nd edn (eds Kaplowitz, N. & Deleve, L. D.) 547–566 (Informa Healthcare USA, Inc., New York, 2007)

[25] National Institutes of Health. National Institutes of Health Consensus Development Conference statement: management of hepatitis C: 2002—June 10–12, 2002. *Hepatology*. 2002;36(5 suppl 1):S3–S20.

[26] Yu, W. C. *et al.* Lamivudine enabled isoniazid and rifampicin treatment in pulmonary tuberculosis and hepatitis B co-infection. *Int. J.Tuberc. Lung Dis.* 10, 824–825 (2006

therapy can decline the probability of hepatic toxic changes. In some cases, antiTB treatment is initiated after antiviral treatment.

Thus, patient with TB and coinfections need to be close observation of health status all the time.

1.3 Multidrug-resistant tuberculosis (MDR-TB).

Multidrug-resistant tuberculosis (MDR-TB), defined as *Mycobacterium tuberculosis* resistant to at least isoniazid (INH) and rifampicin (RMP) (the two most powerful anti-TB drugs), is a rapidly emerging disease characterized by difficulties in treatment (longer, more expensive and with toxic drugs) and high rates of morbidity and mortality, that's why the main efforts to combat and prevent TB in the European Region need to be focused there.

Although many countries have increased efforts to provide MDR-TB treatment, the recent global emergence of extensively drug-resistant tuberculosis (XDR-TB, defined as MDR-TB with resistance to a fluoroquinolone and either kanamycin (KM), amikacin (AMK) or capreomycin (CPM)) has highlighted the possibility that it may be worse to provide inadequate treatment for MDR-TB than to provide no treatment at all.

According to latest report the average proportion of MDR TB cases with XDR-TB is 9.0%. The highest proportions of TB patients with MDR-TB are in Eastern Europe and central Asia. Worldwide, 3.7% of new cases and 20% of previously treated cases were estimated to have MDR-TB.[27]. There has been progress in the detection and treatment of MDR-TB in the last two years. Globally, almost 60 000 cases of MDR-TB were notified to WHO in 2011, mostly by European countries and South Africa.

Achieving universal access to MDR-TB treatment requires a bold and concerted drive on many fronts of TB care, and increased financing. Major efforts are needed to improve treatment success rates among patients with MDR-TB and to reach the level ≥ 75% (the Global Plan target)[28].

1.3.1 MDR-TB as a threat to TB control

In the first Global Plan to Stop TB, four reasons were mentioned for why MDR-TB a threat to TB control: insufficient cure rate for MDR-TB treatment with standardized short-course chemotherapy; high cost of effective therapy; increasing the rates of transmission of MDR-TB and drug-resistant TB without effective treatment; MDR-TB

[27]Global tuberculosis report 2012, WHO, Geneva
[28]Global tuberculosis report 2012, WHO, Geneva

threatens the potential salutary impact of DOTS programmes. Thus, above mentioned identified three areas needing more investment: 1) strengthening laboratory capacity in terms of MDR-TB, 2) defining and operationalizing programmes that can effectively deliver MDR-TB therapy and 3) providing treatment for MDR-TB patients.[29]

1.3.2 Management of MDR-TB

The diagnosis of MDR-TB requires TB patients to be tested for susceptibility to drugs. The *Global Plan to Stop TB 2011–2015* includes targets that by 2015 all new cases of TB considered at high risk of MDR-TB (estimated at about 20% of all new bacteriologically-positive cases globally) and all previously treated cases should undergo DST. Likewise, all patients with MDR-TB need to be tested for XDR-TB.

Globally, only less than 4% of new bacteriologically-positive cases and 6% of previously treated cases were tested for MDR-TB in 2011. In the European Region, 56% of new cases and 27% of previously treated cases were tested for MDR-TB. At the same period in Azerbaijan these figures were 22% and 56% respectevely.[30] ().

1.3.3 Features of MDR-TB treatment regimen

TB treatment requires multiple antibiotics over 6 months or more to achieve cure. In addition, drug-resistant strains of *Mycobacterium tuberculosis* have emerged as a serious problem. The prevalence of MDR *M. tuberculosis* (defined as *in vitro* resistance to isoniazid and rifampicin, the two most potential first-line drugs for TB treatment) is now widely reported.[31][32] MDR strains are currently found in more than 15% of all new cases of TB in some areas of the former Soviet Union (Azerbaijan, Moldova, Ukraine and Tomsk Oblast (Russian Federation)), and in more than 10% in parts of China and other areas of the former Soviet Union (Latvia, Estonia, Kazakhstan, Uzbekistan, and Ivanovo and Mari El (both Russian Federation)).[33] [34] [35]

Strains of *M. tuberculosis* resistant to second-line drugs are also emerging. Cases of extensively drug-resistant (XDR)-TB (defined as *in vitro* drug resistance to isoniazid and rifampicin plus any fluoroquinolone and at least one of the injectable drugs

[29]THE GLOBAL PLAN TO STOP TB 2011–2015.Transforming the fight.Towards elimination of tuberculosis.WHO. 2010.
[30] Azerbaijan. Tuberculosis profile, WHO, 2011
[31]Zignol M, Hosseini MS, Wright A, *et al.* Global incidence of multidrug-resistant tuberculosis. *J Infect Dis* 2006;**194**:479–485.
[32]Aziz MA, Wright A, Laszlo A, *et al.* Epidemiology of antituberculosis drug resistance (the Global Project on Anti-tuberculosis Drug Resistance Surveillance): an updated analysis. *Lancet* 2006;**368**:2142–2154.
[33]Espinal MA, Laszlo A, Simonsen L, *et al.* Global trends in resistance to antituberculosis drugs. World Health Organization/International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. *N Engl J Med* 2001;344:
[34]Raviglione MC, Uplekar MW. WHO's new Stop TB Strategy. *Lancet*2006;367:952–955.
[35] World Health Organization. Anti-tuberculosis drug resistance in the world.Fourth global report. WHO/HTM/TB/2008.394. Geneva, , 2008

(capreomycin, kanamycin or amikacin)) have been described around the globe.[36] [37]. Adverse treatment outcomes for complicated MDR-TB cases (those with additional resistance beyond isoniazid and rifampicin) and cases with XDR-TB occur more frequently than for other cases of TB with lower levels of drug resistance.[38]

1.3.4 Frequencies of resistance to fluoroquinolones among MDR-TB cases.

Fluoroquinolones represent the most powerful class of bactericidal second-line drugs for the treatment of MDR-TB. Patients with MDR-TB and additional resistance to fluoroquinolones have a more serious form of disease compared with those with MDR-TB alone. Their disease is more difficult to treat, and risks evolving into XDR-TB and acquiring resistance to any of the second-line injectable agents. Monitoring resistance to fluoroquinolones in MDR-TB patients is critical to predict the efficacy of second-line treatment and possibly modify the composition of the treatment regimen. Since 2007, WHO has collected surveillance data on cases of MDR-TB with additional resistance to fluoroquinolones, usually ofloxacin, moxifloxacin or levofloxacin.

Data from 62 countries shows, the proportion of MDR-TB cases with additional resistance to fluoroquinolones was 14.5% (95% CI 11.6–17.4%), inclusive of cases with XDR-TB.

WHO's guidelines on treatment of MDR-TB recommend an intensive phase of 8 months and a total duration of 20 months in most patients. There is much less evidence on the effectiveness and safety of regimens of substantially reduced duration and different drug composition, which have been termed short-regimens. This treatment strategy requires close monitoring of the clinical and bacteriological response to treatment for a period of at least 12 months after treatment is completed.

One of the major concerns is that patients who do well after 9–12 months of treatment with less drugs in the continuation phase than in the longer regimen may have a higher risk of acquiring resistance in the process and relapsing.

In most cases, treatment of MDR-TB lasts 20 months or longer, and requires daily administration of drugs that are more toxic and less effective than those used to treat drug-susceptible forms of TB. Success of treatment depends of extention of resistence to anti-TB drugs. According to latest literature review, treatment success of MDR-TB ranged between 35.7% up to 75% of all enrolled patients, while for XDR-TB it

[36]Extensively drug-resistant tuberculosis (XDR-TB): recommendations for prevention and control. *WklyEpidemiol Rec* 2006;**81**:430–432.
[37]Centers for Disease Control and Prevention (CDC)..Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs – worldwide, 2000–2004. *MMWR Morb Mortal Wkly Rep* 2006;55:301–305.
[38] G. Sotgiu**,** G. Ferrara**,** A. Matteelli**,** M. D.Richardson**,** R. Centis**,**S. Ruesch-Gerdes**,** O. Toungoussova**,** J-P. Zellweger**,** A. Spanevello**,** D. Cirillo**,** C. Lange and G. B. Migliori Epidemiology and clinical management of XDR-TB: a systematic review by TBNET**.**

was between 29.3% up to 67%, while 28% of cases were reported as lost to follow-up or had no outcome information [39].

1.4 Other aspects of MDR-TB management

1.4.1 Risk factors impacting on spreading TB and treatment outcome

The development of tuberculosis in humans is a two-stage process in which a susceptible person exposed to an infectious case first becomes infected and second, after an interval of years or decades, may later develop the disease, depending on a variety of factors. Since the acquisition of infection is often far removed from the development of disease and involves different physiologic mechanisms, the risk factors for infection are quite different from the risk factors for *development of disease* following infection[40]. This has important implications for tuberculosis prevention and control.

Existing risk factors influence at catching TB infection as well as TB treatment outcome. The risk of developing disease after infection is strongly age and time dependent and has been reported to be much greater in the 5 years following infection and to decline as the time interval increases[41-42].

Tuberculosis can be found within one family, but it is not clear whether this reflects genetic factors predisposing people to infection and/or disease, shared environmental factors, or the facility of transmission of infection within the home.[43]. Tubercle bacilli can be transmitted during brief contacts between persons who do not live or work together[44]. Thus, it remains unclear whether most transmission of tuberculosis takes place within households or outside of households.

The study, carried out in Absheron rayon of Azerbaijan Republic in period from March to October 2010, provided evidence of substantial effect of main host and environmental factors on the risk of developing tuberculosis. Male sex, 20-29 years age group, basic/none education and secondary education, not having a house/renting house/living in relatives' house, family history of TB and low monthly income are the standout risk factors for TB disease.

[39] G. Sotgiu, G. Ferrara, A. Matteelli, M. D.Richardson, R. Centis,S. Ruesch-Gerdes, O. Toungoussova, J-P. Zellweger, A. Spanevello, D. Cirillo, C. Lange and G. B. Migliori. Epidemiology and clinical management of XDR-TB: a systematic review by TBNET.

[40] Bennett S, Lienhardt C, Bah-Sow O, Gustafson P, Manneh K, Del Prete G, et al. Investigation of environmental and host-related risk factors for tuberculosis in Africa. II. Investigation of host genetic factors. Am J Epidemiol 2002; 155: 1074-9

[41] Vynnycky E, Fine PE. Lifetime risks, incubation period and serial interval to tuberculosis. Am J Epidemiol 2000;152:247–63.

[42] Styblo K. Epidemiology of tuberculosis.(Selected papers, vol 24). The Hague, The Netherlands: Royal Netherlands Tuberculosis Association (KNCV), 1991.

[43] Madico G, Gilman RH, Checkley W, et al. Community infection ratio as an indicator for tuberculosis control. Lancet 1995; 345:416–19

[44] Genewein A, Telenti A, Bernasconi C, et al. Molecular approach to identifying route of transmission of tuberculosis in the community. Lancet 1993;342:841–4.

According to other study age ≥45, male sex, smoking and alcohol usage are main reasons of distribution TB.[45]

Among the other revealed risk factors there are: changing political and social situation (war, economic crisis), HIV infection, inhibitor of cancer necrotic factor (CNF-α) or treatment with interleukin -1. For example, TB risk among the people with AIDS or diminished immunity is 37 times more than among other population.[46]

Some researchers defined malnutrition, smoking, HIV infection, diabetes, alcoholism and contamination of air (gases, dust) are main risk factors for TB infection.[47]

According to the risk factors impacting on treatment, some studies revealed association between MDR-TB treatment outcomes and co-infection. Resistance to two or more antibiotics, a positive sputum result (culture) at the end of initial treatment, cavitary disease, and poor compliance were independently associated with treatment failure.

Some investigators state the possibility of impact of hepatitis B and C co-infections of on MDR-TB treatment outcome. They found out that among patients with pulmonary TB the HBsAg and anti-HCV antibodies was statistically steady. At the same time, both infections in patients with TB were often presented in form of subclinical hepatitis, identified by increase in of aminotransferases activity in blood.[48]

People who live with HIV and inject drugs have a 2-6-fold increased risk of developing TB compared with non-injectors, and commonly have co-morbidities with hepatitis HBV and HCV infection. Among PWIDs who develop TB, at least one in three will also have HIV and two out of three will have HCV antibodies.[49]

But it is still not clear the extent of co-infection HIV, HBV and HCV on MDR-TB treatment outcome, particularly in high risk settings such as prison.

[45] Rao VG, Gopi PG, Bhat J, Yadav R, Selvakumar N, Wares DF. Selected risk factors associated with pulmonary tuberculosis among Sahariatribe of Madhya Pradesh, central India. Eur J Public Health. 2012 Apr;22(2):271-3.
[46] Apvienība HIV.LV 2010. Gada aprīlis ТБ и коинфекция ТБ/ВИЧ в Латвии Краткий обзор ситуации. http://tbpolicy.ru/publications/?id=301
[47] Vərəm xəstələrinin aşkarlanması üzrə klinik protokol.-B.:"CCC Azərbaycan"MMC, 2012.-28 Səh.
[48] Mamedov MK, Rzaeva NR, Dadasheva AE. Epidemiologic peculiarities of infections caused by the hepatitis B and C viruses among lung tuberculosis patients.,Georgian Med News. 2010 Sep;(186):42-6.
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2. Background

2.1 TB in prison: actuality of problem

TB is a major health concern not only in civil sector but also in prisons. it is difficult to calculate the extent to which prisons contribute to the TB burden. However, there are some countries in eastern Europe where TB cases in prisons exceeded 10% of the countrywide total of new TB cases, and in others the notification rate is close to or exceeded 1 000 cases per 100 000 prison population. In some low-incidence countries the higher rate of TB transmission there due to poor control measures and/or the concentration of vulnerable population sub-groups stipulates the higher risk of TB in prisons than in the general population.[50] The risk of TB disease in prisons is on average 23 times higher than the level in the general population.

High prevalence of TB and MDR-TB among offenders is conditioned by several factors. Inmates commonly live in unhealthy settings and do not have the means to, or the habit of, keeping themselves healthy. They may have unhealthy habits or addictions, such as alcoholism, smoking, and drug use, which contribute to their poor health, are risk factors for developing TB, too. For these reasons, they enter prison already ill or with a higher risk of becoming ill compared to the general population. In some countries, while they are incarcerated, prisoners live under harsh and unhealthy environments and suffer from malnutrition, intense psychological and physical stress, and violence. Family relationships are, in many cases, uncertain and deteriorated. These factors can adversely affect prisoners' immune systems and make them more vulnerable to becoming TB or MDR-TB. In some countries there isan unofficial structure in prison, that a powerful structure parallel to official administration has either positive or negative impact on prisoner health.

There were several studies dedicated to revealing factors, exerting on high burden of TB and MDR-TB among the prisoners. It was obvious that some of risk factors related to the environment in prisons can be improved by changing prison infrastructure (e.g. overcrowding, lack of personal bed, limited time in the fresh air, malnutrition and low level of health service quality). Other factors (drug abuse, unsatisfactory situation at home, low economic level) resulted from individual features of prisoners, which cannot be changed by prison's staff.[51] Some studies showed, thatprison's staff (who can be infected and transmit it to family members), discharging

[50] Getahun H, Gunneberg C, Sculier D, Verster A, Raviglione M. Tuberculosis and HIV in people who inject drugs: evidence for action for TB, HIV, prison and harm reduction services. *CurrOpin HIV AIDS* 2012; 7: 345-53)

[51] Gaby E. Pfyffer, Ann iSträssle, Tamara van Gorkum, Françoise Portaels, Leen Rigouts, Christine Mathieu, Fuad Mirzoyev, Hamidou Traore, and Jan D.A. van Embden .Multidrug-Resistant Tuberculosis in Prison Inmates, Azerbaijan. *Emerging Infectious Diseases Vol. 7, No. 5, September-October 2001*

person not adherent to treatment outside of prison can be the source of TB infection. So, TB infection without diagnosis and treatment will move to the society.

MDR-TB in prisons is serious health issue and there are limited number of studies dedicated to investigating risk factors, impacting on MDR-TB treatment outcome among offenders. According to one study, repeated treatment course, bilateral cavities in lungs, massive bacterial loading, male sex, previous imprisonment and alcoholism, resistance to more than seven antiTB medicines, treatment by less than four "active" medicines, positive culture result after the second month of treatment (univariate analysis revealed risk factors, while multivariate analysis defined XDR TB, bilateral cavities in lungs, being students or at the age of pension as predictors of treatment failure).[52]

Analyzing four years treatment results, other study established risk factors of developing XDR-TB during the treatment. There were : treatment in hospital, respiratory distress, bilateral cavities in lungs, previous treatment with second line medicines, missing of more than 20% of all doses (univariate analysis), where multivariate analysis revealed that bilateral cavities in lungs, previous treatment with second line medicines male sex, missing of more than 20% of all doses were predictors of treatment failure.[53]

More than 2 months to culture conversion and bilateral cavitation on chest X-ray were found to be poor outcome risk factors in recent study of MDR-TB treatment outcome in Dominican Republic.[54]

We found just several issue related to failure of treatment TB patients with hepatitis B&C and HIV co-infections and in combination with other conditions.

Guidelines published in 2003 by the American Thoracic Society recommended that tuberculosis patients with epidemiologic factors suggesting a risk for hepatitis B (*eg*, injection drug use, or HIV infection) should undergo a serologic test for detection of this virus.[55]

According to some studies, prisons are well established breeding sites for tuberculosis and HIV infection, especially in settings where no preventive measures are

[52]Leimane V, Dravniece G, Riekstina V, Sture I, Kammerer S, Chen MP, Skenders G, Holtz TH. Treatment outcome of multidrug/extensively drug-resistant tuberculosis in Latvia, 2000-2004.EurRespir J. 2010 Feb 25

[53] Sonya S. Shin, Salmaan Keshavjee, Irina Y. Gelmanova, Sidney Atwood, Molly F. Franke, Sergey P. Mishustin, Aivar K. Strelis, Yevgeny G. Andreev, Alexander D. Pasechnikov, Alexander Barnashov, Tamara P. Tonkel, and Ted Cohen. Development of Extensively Drug-resistant Tuberculosis during Multidrug-resistant Tuberculosis Treatment. Am J RespirCrit Care Med. 2010 August 1; 182(3): 426–432.

[54] Rodriguez M, Monedero I, Caminero JA, Encarnación M, Dominguez Y, Acosta I, Muñoz E, Camilo E, Martinez-Selmo S, de Los Santos S, Del Granado M, Casals M, Cayla J, Marcelino B. Successful management of multidrug-resistant tuberculosis under programme conditions in the Dominican Republic. Int J Tuberc Lung Dis. 2013 Apr;17(4):520-5.

[55]Blumberg HM, Burman WJ, Chaisson RE, et al. American Thoracic Society/Centers for Disease Control and Prevention/ Infectious Diseases Society of America: treatment of tuberculosis. Am J RespirCrit Care Med 2003; 167:603–662

in place and where illicit drug use and drug equipment sharing are common among prisoners. As a result, the risk of becoming infected with the tuberculosis bacillus and the risk of developing active tuberculosis are 26 and 23 times higher, respectively, among prisoners than among members of the general population[56]. The study of treatment outcomes of first 200 DR-TB patients in Azeri prisons revealed Increasing TB/HIV co-infection rate from 3% to 12%, TB/HIV/Hepatitis C from 3% to 10%, steady high TB/Hepatitis C rate on average 63% of DR-TB patients cause significant concerns. It was concluded, that increasing TB/HIV level, high TB/Hepatitis C and TB/HIV/Hepatitis C level is an alarming fact requiring investigations and emergency measures implementation.[57]

Other study dedicated to treatment results and risk factors of patients enrolled to second line drug treatment in penitentiary sector of Azerbaijan. Univariate analysis revealed that cavity in both lungs on integration to treatment was risk factor for unsuccessful treatment outcome, while univariate analysis of co-infection (detected using express HCV test) on integration to treatment as risk factor for unsuccessful treatment outcome has revealed P value = 0.31.[58]

Despite of the high prevalence of hepatitis B&C in prison of Azerbaijan (data of Penitentiary system), substantiality of MDR-TB problem in Azeri prisons, high rate of multidrug resistance[59],it is not clear the extent of impact of HIV, HBV,HCV co-infection on treatment outcome of MDR-TB patients. prison.

Thus, existence of treatment failure among the MDR-TB patients in Azeri prison, possibility of treatment default in patients with hepatitis antigens and limited number of studies of relationship between HIV, hepatitis B&C co-infections and and MDR-TB outcome, stipulate us to conduct study on impacting these co-infection on MDR-TB treatment outcome.

[56]Getahun H, Gunneberg C, Sculier D, Verster A, Raviglione M. Tuberculosis and HIV in people who inject drugs: evidence for action for TB, HIV, prison and harm reduction services. *CurrOpin HIV AIDS* 2012; 7: 345-53)

[57] R.Mehdiyev, E.Gurbanova, F.Huseynov, N.Rahmanov . Results of international approach to TB Control in Prison: Azerbaijan experience. 2012 **42nd Union World Conference on Lung Health,** October 2011, Lille, France

[58] R.Mehdiyev, E.Gurbanova, F.Huseynov, N.Rahmanov. 200 DR-TB patients enrolled on treatment with SLDs in Azerbaijan Penitentiary Sector: treatment results and risk factors. 2012 43rd Union World Conference on Lung Health, November 2012, Kuala Lumpur, Malaysia

[59] Gaby E. Pfyffer, Anni Strässle, Tamara van Gorkum, Françoise Portaels, Leen Rigouts, Christine Mathieu, Fuad Mirzoyev, Hamidou Traore, and Jan D.A. van Embden . Multidrug-Resistant Tuberculosis in Prison Inmates, Azerbaijan..Emerging Infectious Diseases Vol. 7, No. 5, September-October 2001

2.2 TB epidemiology in Azerbaijan

The Republic of Azerbaijan is one of the 18 high TB priority countries of the WHO European Region, with an estimated 11 000 (8 700–13 000) incident TB cases (113 per 100 000 population)(*See Table 3).*

Table 3: Azerbaijan, Tuberculosis profile, 2011

Indicators	Number (thousands)	Rate (per 100 000 population)
Mortality (excluding HIV)	0.34 (0.24–0.44)	3.6 (2.6–4.8)
Prevalence (incl HIV)	16 (7.7–28)	177 (83–306)
Incidence (incl HIV)	11 (8.7–13)	113 (93–134)
Incidence (HIV-positive)	0.16 (0.11–0.22)	1.7 (1.2–2.4)
Case detection, all forms (%)	62 (52–75)	

Source: WHO, 2011

In 2011 a total number of notified cases was 10100 (case notification rate of 100,8 per 100 000 population).Smear and/or culture was positive in 54.2% (2.260 out of 4.166) of all notified new pulmonary TB cases. Among notified re-treatment pulmonary cases 55,7% (1.201 out of 2.124) were smear and/or culture positive.

Overall, the proportion of laboratory confirmed TB cases is very low; only 39.1% of all notified TB cases had a positive smear microscopy result in 2011 (*Table 4*).

Table 4: Case finding by patient category (reporting period 2011)

TB case category		All cases	% All
New cases		5 296	52,4
	Smear + & Pulmonary TB	1 426	14,1
	Smear - & Pulmonary TB	2 740	27,1
	Extra-pulmonary TB	1 130	11,2
Previously treated smear + & PTB cases		2 124	21,0
	Relapse	1 202	11,9
	Treatment after interruption (Defaulters)	266	2,6
	Treatment after failure	656	6,5
Other cases		2 680	26,5
Total		10 100	100,0

Source: NTP annual report to WHO, 2012

2.3 Infrastructure of TB control services

The MoH has the overall responsibility for TB control in the country. It undertakes this function through the National Tuberculosis Program (NTP). The NTP is represented by the monitoring and evaluation (M&E) unit, the diagnostic and treatment unit that

includes the NRL, the central warehouse for anti-TB drugs, an office manager and a financial manager. TB control interventions are delivered through a network of specialized TB service institutions functioning under the MoH. There are total of 69 specialized TB institutions. TB services in Baku city are represented by the Scientific Research Institute of Lung Diseases (SRILD), a hospital for MDR-TB with 75 beds, six TB dispensaries and three TB cabinets in primary health care services (PHC), i.e. city policlinics.

The National TB Program of Azerbaijan adopted DOTS as a national strategy for TB control, achieved the full coverage by 2005. The diagnosis of TB is established by X-ray and direct sputum smear microscopy. Case classification and definition of treatment category are done in the specialized TB service institutions. The majority of infectious TB patients are hospitalized during the intensive phase of treatment. The X-ray findings, instead of history of previous treatment, are used for determining the treatment regimen (inclusion of streptomycin in the regimen). The doses of anti-TB drugs are chosen according to the WHO-recommendations.

2.4 The effectiveness of TB treatment in Azerbaijan

İn 2010 in Azerbaijan the treatment success rate among new pulmonary smear positive and among all previously treated TB cases was 76.6% and 62.3%, respectively (*Table 5***)**. High default rates of 10.8% among new smear positives and 15.3% among all previously treated cases, contribute to the low treatment success rate. In addition, the proportion of not evaluated cases, the so-called “transfer out” category is significant - 15.4% - among previously treated TB cases notified in 2010 (See *Table 5*).

Table 5: Treatment outcomes of new smear positive- and previously treated smear positive and smear negative adult (cohort study, 2010)

Treatment outcome	**New smear + cases**		**Previously treated cases**	
	Number	%	Number	%
Total number of cases reported	1 733	100	4 000	100
Total number of cases evaluated	1 733	100	4 000	100
Cured	753	43,5	494	12,4
Treatment completed	574	33,1	1 998	50,0
Died	60	3,5	127	3,2
Failure	66	3,8	153	3,8
Default	188	10,8	611	15,3
Transfer out	92	5,3	617	15,4
Treatment success rate (Cured & treatment completed)	1 327	76,6	2 492	62,3

2.5 Situation with MDR-TB in Azerbaijan

Only anti-TB Drug Resistance Survey (DRS) conducted between August 2006 and June 2007 and included civilian and penitentiary systems, revealed very high levels of drug resistance; 22.3% (95% CI 19-26) MDR-TB among new cases and 55.9% (95% CI 52-60) among previously treated TB cases. XDR-TB was found in 12.8% of all identified MDR-TB cases. Today, Azerbaijan is still among the 27 high multidrug-resistant (MDR) TB burden countries in the world with the third highest MDR-TB rate worldwide with estimation 22% of all new TB cases and 56% of retreatment cases. 55% of new cases and 35% of retreatment cases had been confirmed in laboratory (WHO, 2011).

Methods for rapid diagnosis of MDR-TB are available at the National Reference Laboratory and in the penitentiary system, but not routinely accessible in most territory of the country. The laboratory network therefore needs further strengthening in order to scale up the new diagnostic methods and expansion of culture and drug susceptibility testing.

2.6 TB situation in penitentiary system of Azerbaijan

The Main Medical Department of the MoJ carries out regular screenings for inmates and people on remand, starting from trial isolators in the framework of the TB control project in the penitentiary system. The compulsory diagnostic algorithm consists of a questionnaire and X-ray investigation. Sputum samples from suspicious TB cases are taken for microscopy and bacterial inoculation. Rapid diagnostic sensitivity tests are run routinely based on the latest diagnostic technologies. Suspected and/or confirmed cases of TB are immediately isolated in separate rooms and within several days (not later than a week) are transferred to a specialized treatment institution under the Ministry of Justice where all forms of TB, including drug-resistant TB, are treated. In this closed medical institution, treatment is available for all inmates and people under investigation without regard to sex, age, inside regime mode and conditions of punishment.

Situation analysis on TB control in penitentiary system, embodied by ICRC in 2001, revealed that MDR-TB was a serious problem among prisoners, who was detected Beijing strain of *M. Tuberculosis,* but it was impossible to identify the reason and type of development.[60]

[60]Verma, S. & Kaplowitz, N. In *Drug-Induced Liver Disease* 2nd edn (eds Kaplowitz, N. & Deleve, L. D.) 547–566 (InformaHealthcare USA, Inc., NewYork, 2007).

After the visit of Azerbaijan prisons by ICRC authorities 1995, the ICRC addressed its financially and technically support to reducing the number of TB cases in detention centers by improving screening, prevention, treatment and follow-up.

Within last few years' government of Azerbaijan, represented by MoJ and international organizations (e.g. Global Fund against TB, AIDS and Malaria) have conducted a lot of important events for improving situation with TB infection in prisons by improving the detection TB and quality and efficacy of treatment. Being implemented since 2007 such large-scale actions include equipping labs with modern technologies, enrolling detainers to treatment and follow up this procedure after discharging.

The ICRC also provided technical support to start a pilot project for treatment of patients suffering from MDR-TB. So, to 2006, over 7,750 TB treatments were provided to the affected detainees, and of them 3,874 treatments have been successfully completed.[61]

Moreover, as an effective strategy to stop TB the DOTS (Directly Observed Treatment Short-course) strategy for the first time in Azerbaijan was launched by MoJ in 1995 with ICRC technical assistance and government consistent support. SLD treatment has been performed in penitentiary sector since 2007.

In order to strengthen treatment adherence among released TB patients a memorandum of understanding was signed in 2009v between MoH through NTP, MoJ and ICRC on piloting follow –up of DR-TB patients after release from prisonTB hospital without completing their treatment in prison. After coming to end in 2010 this initiative has been continued by local NGO "Support to Health" within the frame of GFATM grant. Thus, currently NGOs manage to follow up 98% of released patients As a result of patient support program default rate is significantly reduced, management of the continuum of care in this way is not sustainable.[62]

According to statistic data from penitentiary system, sensitive (regular) TB have been diagnosed in 254 out of 793 patients involved into the treatment in 2009 by means of sputum smear test. The number of diagnosed patients were increased in favor to high efficacy of detection method (in 2008 these indicators were 746 and 287 respectively).[63]

Table 6: Annual treatment outcomes of MDR-TB patients enrolled to study

Patient group		Cured	Treatment completed	Failed	Interrupted treatment	Died	Transfer out	Still on treatment	To

[61]ICRC Resource centre ,http://www.icrc.org/eng/resources/documents/update/azerbaijan-update-311206.htm

[62] R. Mehdiyev, E. Gurbanova, A. Ismayilov Two of DS-TB patients re-imprisoned and continued treatment in prison; 51 of them finalised, 2012.. *43rd Union World Conference on Lung Health, November 2012, Kuala Lumpur, Malaysia*

[63]AzR Ədliyyə nazirliyinin Baş Tibb İdarəsi, 2010

New	2007	1	0	0	0	1	0	0	2
	2008	0	0	0	0	0	0	0	0
	2009	13	0	1	2	0	0	0	16
Previously treated with FLD only	2007	22	0	5	0	1	0	0	28
	2008	22	0	1	6	2	0	0	31
	2009	41	0	3	1	3	0	0	48
Previously treated with both	2007	26	0	4	2	4	0	0	36
	2008	13	0	4	4	2	0	0	23
	2009	24	0	3	3	2	0	0	32
Total	2007	49	0	9	2	6	0	0	66
	2008	35	0	5	10	4	0	0	54
	2009	78	0	7	6	5	0	0	96
%	2007	74,2%	0,0%	13,6%	3,0%	9,1%	0,0%	0,0%	10
	2008	64,8%*	0,0%	9,3%	18,5%	7,4%	0,0%	0,0%	10
	2009	81.2%	0.0%	7.3%	6.3%	5.2%	%	%	10

Source: AzR Ədliyyə nazirliyinin Baş Tibb İdarəsi,

2.7 Importance of study on TB risk factors in prisons

In Azerbaijan there were only some studies on risk factors contributing to spreading TB and influencing on TB treatment outcomes in prisons. It was revealed that resistance to two or more antibiotics, a positive sputum result at the end of initial treatment, cavity disease, and poor compliance were independently associated with treatment failure, and first-line therapy may not be sufficient in settings with a high degree of resistance to antibiotics.[64]

Other study also showed the high prevalence of hepatitis B and C among patients with lung TB. The frequency of revealing of these hepatitis markers in patients with chronic TB is considerably higher than its frequency in patients with acute TB. İt

[64] R. Mehdiyev, E. Gurbanova, A. Ismayilov Two of DS-TB patients re-imprisoned and continued treatment in prison; 51 of them finalised, 2012.. ***43rd Union World Conference on Lung Health,*** *November 2012, Kuala Lumpur, Malaysia*

was noted, that both infections were often presented as subclinical hepatitis, that is usually identified by increasing of aminotransferase's activity in blood.[65]

Thus, investigating of risk factors of TB in closed society such as the prison can contribute to increasing efficacy of programs towards decreasing TB mortality and morbidity. The importance of the study risk factors in prisons is determined by the follow reasons: lack of knowledge about the impact co-infections and other risk factors on MDR TB; wide spread of MDR-TB in prisons. insufficiency of measures to prevent MDR –TB expansion among prisoners. Moreover, the risk of getting TB and its distribution is higher in prisons than in the general population. It can be explained by high rate of TB transmission there due to poor control measures and/or the concentration of vulnerable population sub-groups, living in unhealthy settings, having unhealthy habits or addictions, such as alcoholism, smoking, and drug use, which contribute to their poor health and are risk factors for developing TB, too. For these reasons, they enter prison already ill or with a higher risk of becoming ill compared to the general population. In some countries, while they are incarcerated, prisoners live under harsh and unhealthy environments and suffer from malnutrition, intense psychological and physical stress, and violence. Family relationships are, in many cases, uncertain and deteriorated. These factors can adversely affect prisoners' immune systems and make them more vulnerable to becoming ill with multiple diseases.

Thus, Identifying risk factors in prisons and their prevention can impact on decreasing TB load in society.

[65] Mamedov MK, Rzaeva NR, Dadasheva AE. Epidemiologic peculiarities of infections caused by the hepatitis B and C viruses among lung tuberculosis patients.,Georgian Med News. 2010 Sep;(186):42-6

3. Methods and Materials

3.2 Methodology

3.1.1 Context

The importance of the research has been determined by the lack of knowledge about the impact of co-infections and other risk factors on MDR -TB treatment, particularly among prisoners. Prevalence of HIV and hepatitis C among the prisoners is higher than among the general population due to some features of their social status. However, the knowledge about association between co-infections and other risk factors and MDR-TB treatment outcome is still limited.

3.1.2 Objective

To reveal the extent of association co-infections HIV and hepatitis B and C with MDR-TB treatment unfavorable outcome among prisoners admitted to the Specialized Medical Unit of Penitentiary System of Azerbaijan.

3.2 Design and Settings

The study covered prisoners with MDR-TB and hepatitis B&C (seropositive) and HIV co-infections , who had their treatment with second line medicines during April 28th 2007 and December 16th 2010 year (289 cases),out of which75.8% (219) –cured, 17% (49)-died or failure, 7.2% (21) - non-completed (defaulted or transfer out). Analyzing risk factors we focused on 268 patients that completed treatment as Inclusion criteria.

The blood analysis to detect HIV has been performed at the National AIDS center by using IFA method.

HCV test was done by Rapid Chromatographic Immunoassay for the qualitative detection of antibody to HCV; HBV was examined by Rapid Chromatographic Immunoassay for the qualitative detection of HBV Ag (examination of HCV and HBC was conducted in Specialized Medical Unit of Penitentiary System of Ministry of Justice

Examination of blood for antibodies to hepatitis B and C co-infection revealed that 66.2% of patients were seropositive, among which 4.4% person had hepatitis B co-infection, while 90.7% patients had hepatitis C co-infection, and just 4.9% had combination of both co-infection. In contrary, HIV|AIDS was revealed in just 5.5% (16) patients with MDR-TB, half of which received ARV therapy. Appointment of chemotherapy regimen, as well as monitoring and evaluation of treatment outcomes for all patients was carried out on the basis on information about susceptibility to the drugs of the first and second line, previous treatment, and it was made in strict accordance with international standards on treatment of MDR-TB patients, adopted by WHO.

Having divided prisoners into group with successful treatment outcome and group with poor outcome, we tried to find risk factors predicted these outcomes.

Risk factors revealing from comparing two groups underwent to univariate analysis, that defined their OR and the role of these risk factors in MDR-TB treatment outcome.

3.3 Data analysis

Provided data file was transferred from Epi Info format to Stata v. 12 format and preparation data for analysis (data cleaning and data verification) was done in statistical package Stata v. 12 as well. The main variable (dependent) with two categories, "favorable treatment outcome" and "poor treatment outcome" was created from existed variable "final treatment outcome", which had following categories: "cured", "died", "defaulted", and "failed". "Cured" included in "favorable treatment outcome"; "died" and "failed" in "poor treatment outcome" categories. "Defaulted" cases were not included in the analysis.

In order to describe possible risk factors descriptive analysis was conducted for each variable. For categorical variables we extracted percentages and for continuous variables median and range. For the final model all continuous variables were converted into dichotomous variable taking cutoff point from the median (except for BMI where cutoff point was 18.5).

The relationship between key independent variables (risk factors) and dependent variable (treatment outcome) was tested by using Chi-square test. The significance of relationship was tested by p level 0.05, which is the minimum requirement for statistical significance with 95% confidence interval.

Based on available literature that suggest model building strategies for multivariate regression, variables associated with treatment outcome with significance level $p \leq 0.25$[66] were included in the analysis. Since our dependent variable is dichotomous multiple logistic regressions conducted for the purposes of this study. The dataset passed all necessary diagnosis including the specification error[67], goodness-of-fit[68], multicollinearity[69] and influential observations[70] .

Due to small variance in variables "contact with MDR patients", "HIV", "tobacco use", "diabetes", "no cavity", "Ofx", "hearing loss", "nausea" and "hypomagnesaemia" as side effect of 1st and 2nd line drugs" were not included in the final model. These

[66] Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiley & Sons; 2000.
[67] Linktest was not significant. _hatsq, b=-.029 . Z=-0.22. p>0.825
[68] Goodness of fit test was not significant. chi2(83) = 69.62, p > 0.86
[69] High VIF (variance inflation factors) was not found.
[70] Outliers that can impact the overall result was not observed.

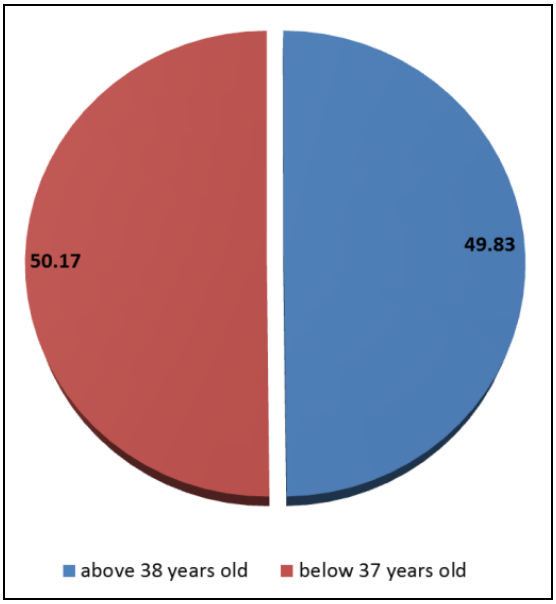
variables did not meet requirement of having at least 5% observation in each cell. However, before removing those variables from the model Wald Test was conducted in order to test the significance of a subset of coefficients of omitted variables and they were not significant with very high p value.

4. Results

The study covered prisoners with MDR-TB and hepatitis B&C (seropositive) and HIV co-infection , who had their treatment with second line medicines during April 28th 2007 and December 16th 2010 year (289 cases), out of which75.8% (219) –cured, 17% (49)-died or failure, 7.2% (21) - non-completed (defaulted or transfer out). Analyzing risk factors we focused on 268 patients that completed treatment as Inclusion criteria.

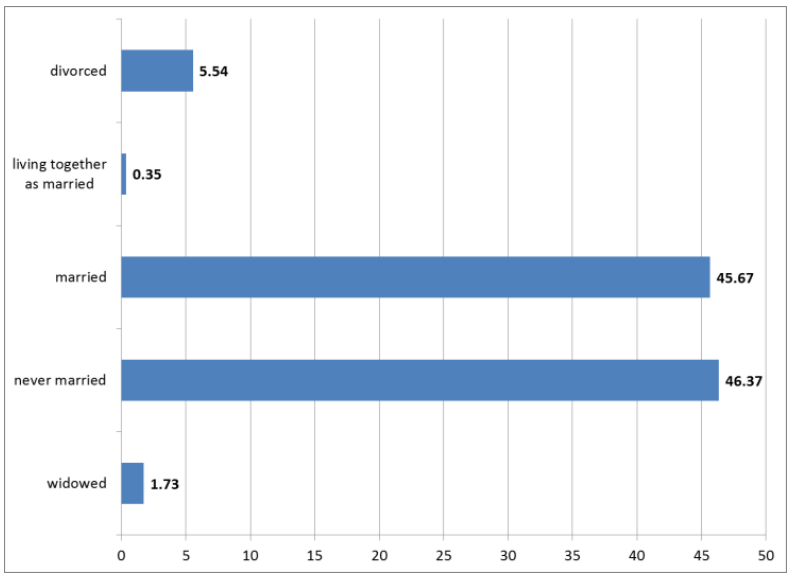
All study population consisted of male with median age 37 (age ranged from 19 to 57 y.o). In general, 49.8% (144) of all participants were above 37 years old and 50.2% (145) below 37 years old (median) (*See Figure 1*).

Figure 1: Age distribution of the patients (%)



By marital status 46.4% (134) of patients never been married, 45.7% (132) were married, and 5.5% (16) were divorced (*See Figure 2*).

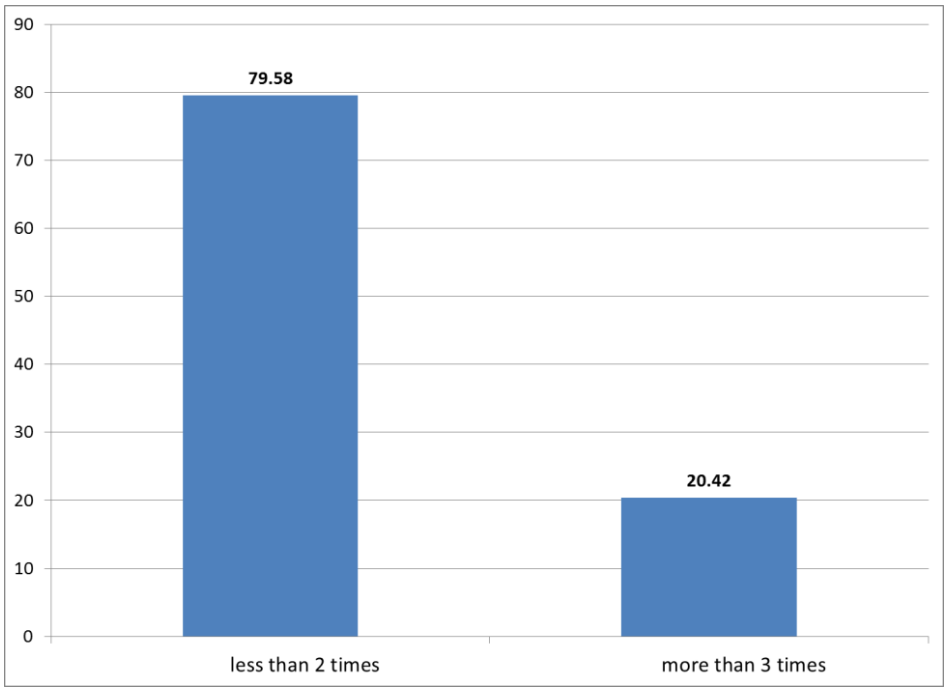
Figure 2: Marital status of patients (%)



As for non-medical risk factors, “the number of convictions” significantly affects on the results of treatment –, but it is difficult to interpret. Most likely, the reason is the regime for prisoners. A large number of convictions, as a rule, prisoners with shorter prison terms of punishment, that is, relative to the “not heavy” crime, do not require cell-contents. This indicates that the effect is not only the number of convictions, but also the duration of detention and conditions of the patients.

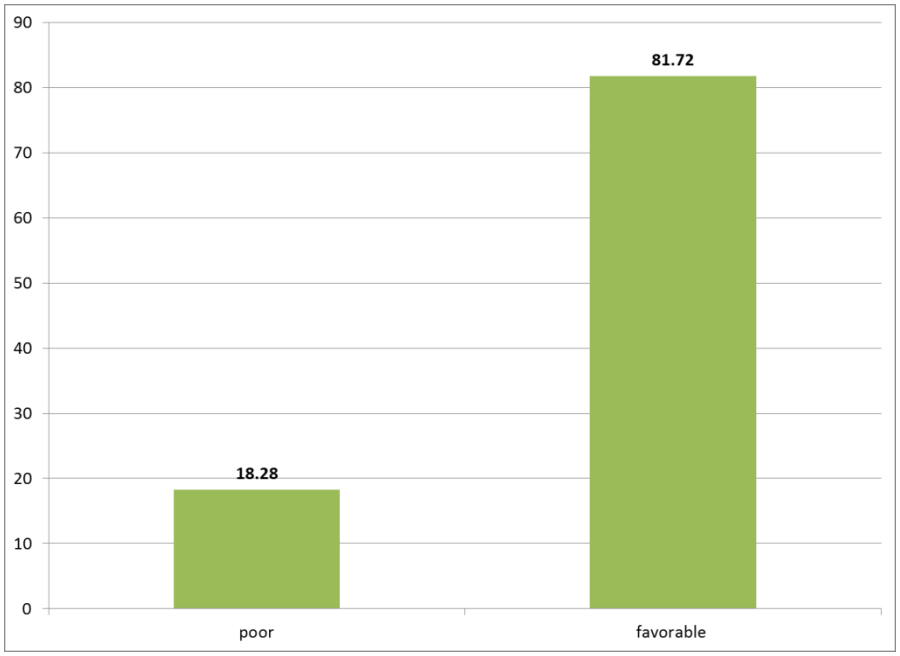
The median years of imprisonment for all patents were 2 years with the range of 1-7 years. Analysis of frequency of imprisonment revealed that 20.4% (59) of them had imprisoned for the third time and more and 79.6% (230) for the second time or less (*See Figure 3*).

Figure 3: Total number of imprisonment (%)



Using the adherence to full course of treatment as the main criteria for cohort selection, we narrowed the surveyed patients up to 268 people and in analysis used the data from above mentioned ones. The study showed that results of treatment with second line medicine had “unfavorable treatment” in 18.3% (49) of patients, while 81.7% (219) of patients was “cured” (S*ee Figure 4)*. 30.1% (87) of patents did self-treatment before involving in treatment process in prison.

Figure 4: Treatment outcome of patients (%)



As medical risk factors contact with diseased person has not been investigated enough, because most of patients either did not know, or did not remember if they were in contact with MDR patient before, and only 4.5% (13) patients confirmed their previous contact with MDR patient.

The blood analysis to detect HIV has been performed at the National AIDS center by using IFA method.

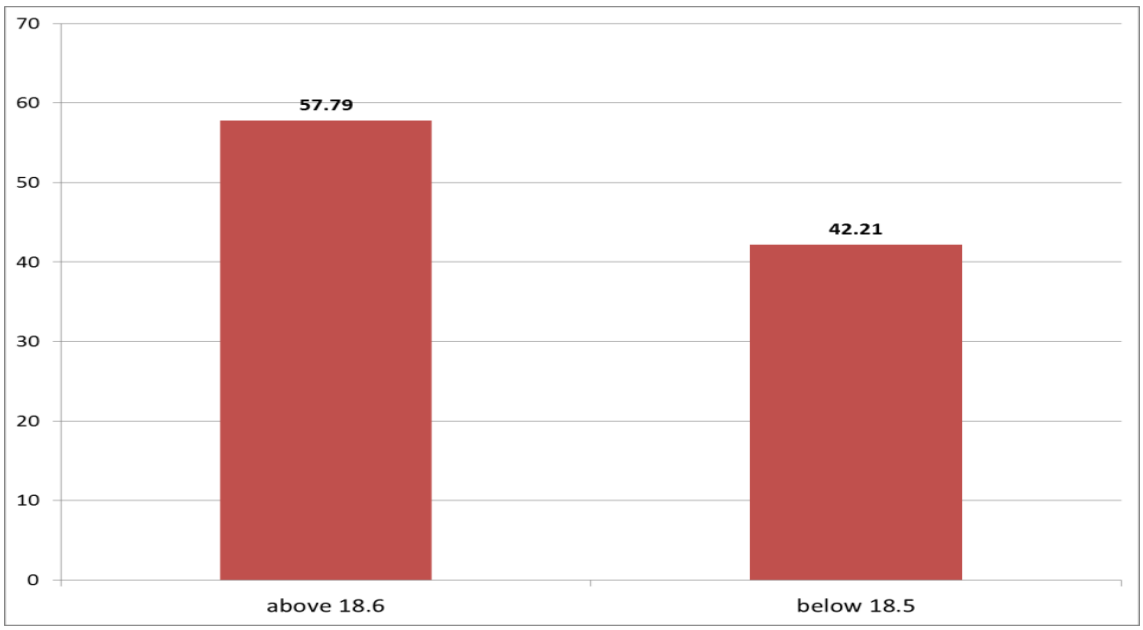
HCV test was done by Rapid Chromatographic Immunoassay for the qualitative detection of antibody to HCV; HBV was examined by Rapid Chromatographic Immunoassay for the qualitative detection of HBV Ag (examination of HCV and HBC was conducted in Specialized Medical Unit of Penitentiary System of Ministry of Justice

Examination of blood for antibodies to hepatitis B and C revealed existing hepatitis coinfections in 204 (66.2%) patients with MDR-TB, among which 9 (4.4%) person had hepatitis B, while 185 (90.7%) patients were seropositive for hepatitis C, and just 10 (4.9%) out of all had combination of both viruses antibodies.

In contrary with the wide distributing of hepatitis viruses, HIV|AIDS was revealed in just 16 (5.5%) patients with MDR-TB, half of which received ARV therapy, necessary to did notice that all these patients were included in the group with “success”. However, the small size of group of MDR-TB patients with HIV|AIDS co-infection required further investigation of HIV|AIDS impact on MDR-TB treatment outcome. Investigating behavioral risk factors revealed that 29.8% (86) of patients were drug users and 97.6% (282) were tobacco users.

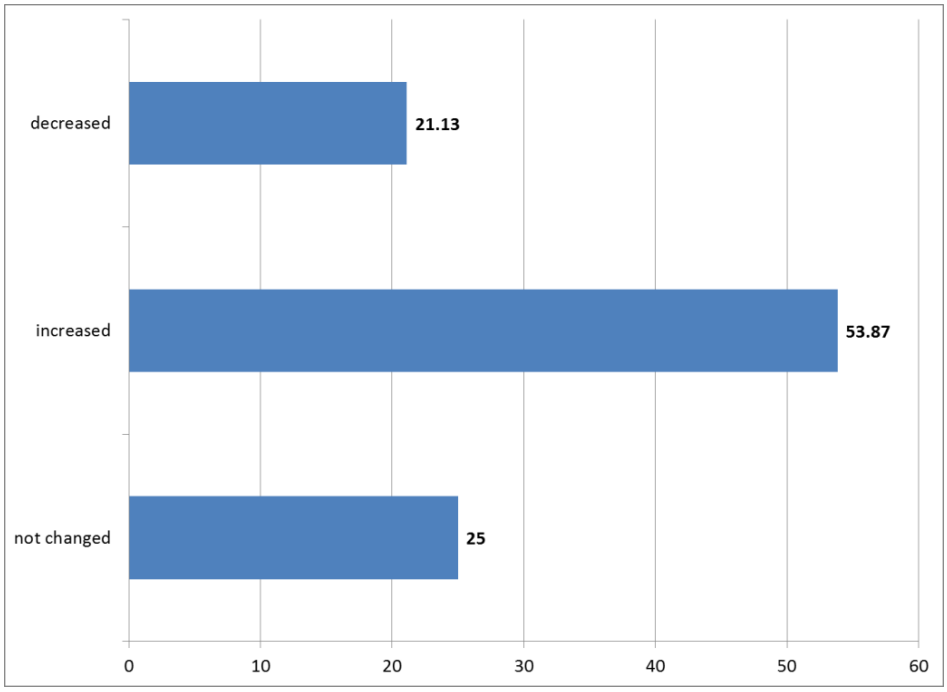
Before initiating the treatment the index of the growth/weight (BMI) was below normal (the cutoff BMI point was 18.6) in 42.2% (122) of patients, and was above cut off in 57.8% (167) of patients. The median BMI score of patients in the beginning of treatment was 19.3 (the range was 13.9-28.9) (*See Figure 5*).

Figure 5: BMI status of patients in the beginning of the treatment (%)



Study revealed that within first 6 months of treatment BMI score of 53.9% (153) of patients increased, for 21.1% (60) decreased and of 25.0% (71) did not changed (*See Figure 6*).

Figure 6: BMI status change after 6 months (%)



Pretreatment plain CX-ray of patients showed that 41.5% (120) of them had cavity in one lung, 44.6% (129) had cavity in both lungs, while 13.8% (40) did not have any cavity.

Smear sputum microscopy and culture test before starting the treatment revealed that just 4.5% (13) of patients had SS-/C+result, while the remain detainers was SS+/C+.

Sputum smear results of 80.97 (234) of patients were positive before starting the treatment. Sputum smear results of 40.4% (116) of patients was positive in the first month of treatment and of 30.0% (85) in the second month of treatment.Culture results in the first month was positive for 59.7% (163) of patients and for 38.95% (104) it was positive in the second month. In other words the percentages of positive sputum smear result and culture result decreased in the second month of treatment. Taking into account above mentioned, it was concluded, that dynamics of sputum conversation was progressive from the beginning of treatment.

Resistance to fluoroquinolones in MDR-TB patients is critical to predict the efficacy of second-line treatment, and in our study it was found, that in addition to other drugs, 12 (4.2%) patients had any resistance to Ofx, that had been enrolled to DOTS+ treatment. There were just three patients with XDR-TB, out of which 1 case – cured, 1 case – died, 1 case - voluntary default.

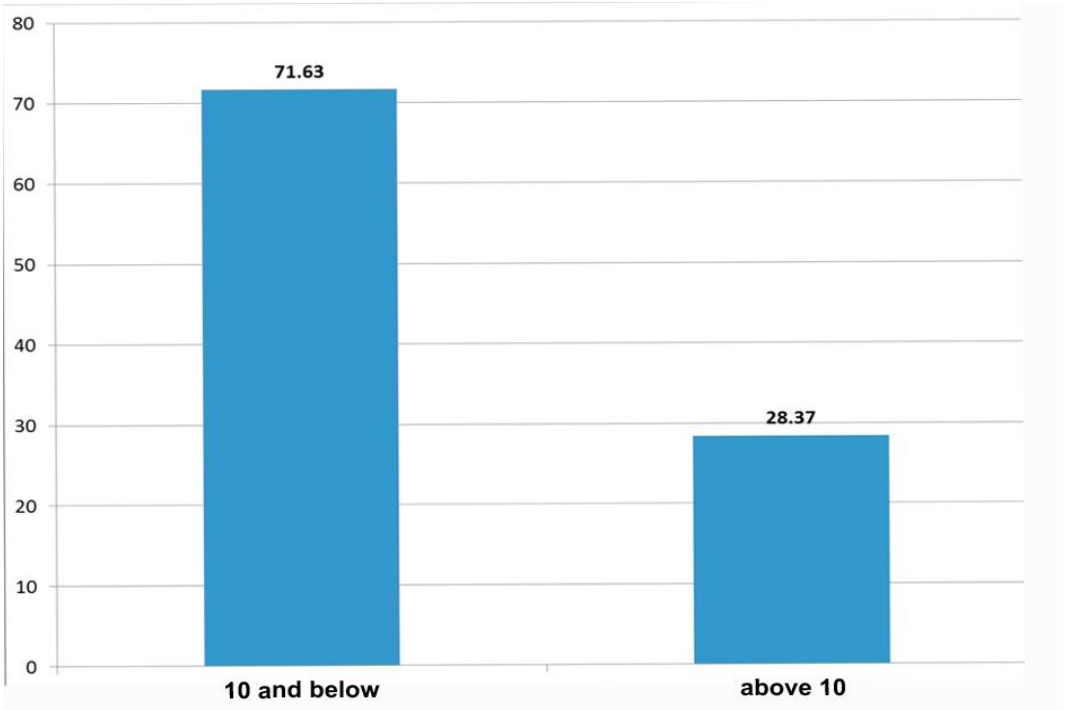
The severity of the patient evaluated on a set of indicators. The degree of severity is formed by the estimation of the following points *(See Table 6)*.

Table 7: Criteria the degree of severity

Sign	Points
Bilateral involvement in process	**1**
Cavity TB	**2**
Infiltrative TB	**1**
Milliar TB	**2**
Associated pleural effusion/ pleural empyema	**2**
SS-/C+	**1**
SS+/C+	**2**
Resistance to FLD	**1**
Resistance to FLD	**2**
Resistance to Ofx or Cm	**1**
High temperature	**1**
Low Hb level	**1**
Low BMI (< 18.6)	**1**

We found, that the median score of disease severity marker was 10 (with the range of 4-14). More than 10 points gained one third of patients - 28.4% (82), while 71.6% (207) had 10 points and below (*See Figure 7*).

Figure 7: Disease severity markers (%)



Characteristics of study population were summarized in the *Table 7*.

Table 8: Description of study population

Characteristics (n, if not 289)	**n (%)**	**Median (range)**
Age		37 (19-57)
above 38 years old	144 (49.8)	
below 38 years old	145 (50.2)	
Marital status		
Divorced	16 (5.5)	
living together as married	1 (0.4)	
Married	132 (45.7)	
never married	134 (46.4)	
Widowed	5 (1.7)	
Total number of imprisonment		2 (1-7)
below 2	230 (79.6)	
above 2	59 (20.4)	
Treatment outcome (n=268 excluding lost of follow up)		
Poor	49 (18.3)	
favorable	219 (81.7)	
Self-treatment on previous stage of treatment	87 (30.1)	
Contact with MDR (n=287)	13 (4.5)	
HIV positive	16 (5.5)	
Hepatitis (total)	204 (66.2)	
Hepatitis C	185 (90.7)	
Hepatitis B	9 (4.4)	

Hepatitis B & C	10 (4.9)	
Drug abusing (in the past)	86 (29.8)	
Tobacco use	282 (97.6)	
Diabetes	11 (3.8)	
BMI		19.3 (13.9-28.9)
above 18.6	167 (57.8)	
below 18.6	122 (42.2)	
BMI change after 6 months(n=284)		
Decreased	60 (21.1)	
Increased	153 (53.9)	
not changed	71 (25.0)	
Existence of cavity in lungs		
No cavity	40 (13.8)	
Cavity in one side	120 (41.5)	
Cavity in both sides	129 (44.6)	
Conversion of sputum culture		
Positive smear result before the treatment	234 (80.97)	
Positive smear result 1st month (287)	116 (40.4)	
Positive smear result 2nd month (287)	85 (30.0)	
Positive culture result 1st month (273)	163 (59.7)	
Positive culture result 2nd month (267)	104 (39.0)	
Resistance to Ofx (ofloxacin)	12 (4.2)	
Disease severity markers (in points)		10 (4-14)
below 10	207 (71.6)	
above 10	82 (28.4)	

Heavy side effects of anti-TB medicines are considered as reason to stop follow up to treatment. We revealed, thatamong side effects of chemotherapy with first and second line medicine, which significantly influenced on the general condition of patients toxic hepatitis – in 51 (27.3%), headache – in 21 (11.2%), dizziness 17 (7.5%), nausea 30 (16.0%), and abdominal pain 15 (8.0%) of patients were with higher frequency (*See Table 8*).

Table 9: Side effects of 1st and 2nd line drugs ( )

Side effects	n (%)
Headache (187)	21 (11.2)
Dizziness (187)	17 (7.5)
Seizures (182)	1 (0.5)
Peripheral neuropathy (186)	3 (1.6)
Hearing loss (187)	3 (1.6)
Psychotic symptoms (187)	32 (17.1)
Depression (187)	2 (1.1)
Nausea (187)	30 (16.0)
Vomiting (187)	6 (3.2)
Diarrhea (187)	7 (3.7)
Abdominal pain (187)	15 (8.0)
Skin rash (187)	4 (2.1)
Arthralgia (187)	28 (15.0)
Allergy (187)	2 (1.1)
Hepatitis (187)	51 (27.3)
Hypomagnesaemia (187)	5 (2.7)

Sleeplessness (187)	6 (3.2)

4.1 Factors associated with treatment outcome

The univariate statistical analysis of risk factors for treatment failure in patients with MDR-TB identified (*See Table 10*) several variables significantly ($p<0.05$) associated with poor outcome, those are: total number of imprisonment, contact with MDR patients, diabetes, low BMI at start of treatment, existence of cavities in both lungs, positive smear result before the treatment, positive smear and culture results in the first and second months of treatment, resistance to Ofx, disease severity markers 10 and more than 10 points, side effects of 1st and 2nd line drugs such as hearing loss and hypomagnesaemia. Other factors such as presence of one cavity in one lung, disease severity markers less than 10 points, high BMI (>18.5) at the start of treatment, positive smear and culture results in the first, and negative results in the second months of treatment were significantly associated with successful treatment outcome.

Table 10: Factors associated with treatment outcome

Characteristics	Patents with poor outcome (n=49)% (n)	Patients with successful outcome (n=219) %	p value
Age			
above 38 years old	49.0 (24)	50.2 (110)	0.874
below 37 years old	51.0 (25)	49.8 (109)	
Marital status			
Divorced	2.0 (1)	5.9 (13)	0.727
Married	42.9 (21)	46.6 (102)	
Single	53.1 (26)	45.2 (98)	
Widow	2.0 (1)	2.8 (6)	
Total number of imprisonment			
below 2	91.8 (45)	77.6 (170)	0.024
above 3	8.2 (4)	22.4 (49)	
Self-treatment	32.7 (16)	28.3 (62)	0.545
Contact with MDR	10.2 (5)	3.2 (7)	0.034
HIV positive	2.0 (1)	6.9 (15)	0.199
HBV/ HBC co-infection	61.2 (30)	65.3 (143)	0.590
Drug abusing (in past)	24.5 (12)	32.4 (71)	0.278
Tobacco use	93.9 (46)	98.2 (215)	0.088
Diabetes	8.2 (4)	2.3 (5)	0.039
BMI			
above 18.6	36.7 (18)	62.6 (137)	0.001
below 18.5	63.3 (31)	37.4 (82)	
BMI change after 6 months			
Decreased	23.9 (12)	18.8 (41)	0.550
Increased	47.8 (23)	56.4 (124)	
not changed	28.3 (14)	24.8 (54)	
Existence of cavity in lungs			
No cavity	4.1 (2)	16.0 (35)	0.029
Cavity in one side	28.6 (14)	46.6 (102)	0.021
Cavity in both sides	67.4 (33)	37.4 (82)	0.000
Conversion of sputum culture			

Positive smear result before the treatment	45 (91.84)	169 (77.17)	0.021
Positive smear result 1st month	56.3 (28)	36.1 (79)	0.010
Positive smear result 2nd month	46.8 (23)	24.9 (54)	0.003
Positive culture result 1st month	80.4 (39)	54.6 (119)	0.001
Positive culture result 2nd month	73.3 (36)	29.4 (64)	0.000
Resistance to Ofx	14.3 (7)	1.83 (4)	\0.000
Disease severity markers (in points)			
below 10	44.9 (22)	78.5 (172)	0.000
above 11	55.1 (27)	21.5 (47)	

Variables with bold highlight are included in multivariate analysis.
** Highlighted with yellow are not included in multivariate analysis as assumption having 5% at least in each cell was not met. Even if we include them statistical software automatically omitted them.*

The univariate analysis revealed, that frequency of imprisonment had impact on treatment result, and 77.6% of "cured" patients had imprisoned twice or less, while 91.8% of patients with poor result had the same frequency of imprisonment, which confirmed the relationship between total number of imprisonments and treatment outcome.

It doesn't mean that less imprisonment frequency leads to best treatment! Based on data specialists from penitentiary system explained, that patients with less imprisonment frequency, had long term life in prison with heavy regimen.

Remembering that TB is airborne infection and considering the contact with diseased person as a risk factor, we found, that just 3.2% of "cured" patients with reported their contact with MDR-TB patients, while proportion of such patients among those with poor result was 10.2%. Despite of insufficient investigating of this risk factor (only 4.5% (13) respondents could confirm their contact with diseased person), above mentioned concluded the existence association between contacts with MDR-TB patients and treatment outcome.

Diabetes makes the person immune system more susceptible to infections. The study confirmed the fact again by discovering diabetes in 8.2% of patients with poor result and in 2.3% of "cured" patients

TB as a sociable pathology proportionally related to the nutritional status of persons, and the statement was repeatedly verified in the study. According to the defined cutoff at the 18.5, the index of the growth/weight (BMI) often was below normal in 63.3% of patients with "failure" of treatment, than in a patients with "treatment success" – 37,4%, however, during the first six months of treatment BMI did not change significantly in both group of patients.

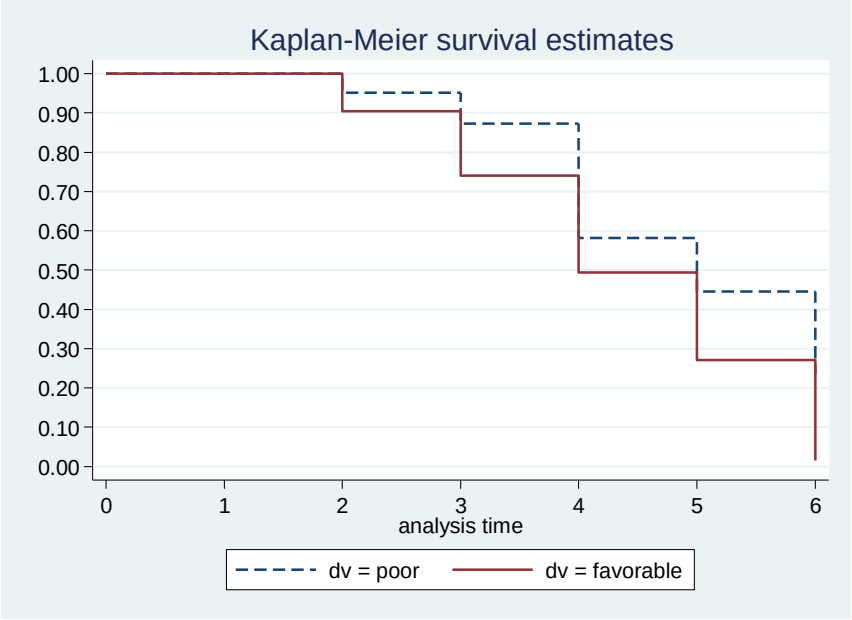
Considering the prevalence of tuberculosis unilateral as well as bilateral cavities in lungs as significant factors influencing on treatment results of patients with MDR-TB, the study established, that 46.6% of patients with "treatment success" and 28.6% of

patients with “failure” treatment had unilateral cavity, while 67.4% of patients with “failure” treatment and 37.4% of patients with recovery had bilateral destructive processes.

The time of sputum conversion is one of the precursors of efficacy and outcome of treatment. The positive result of sputum smear microscopy in the first and second months of treatment was more common in patients with poor result than “cured” patient The results of sputum culture were also significantly more frequently positive on the first and second months of treatment in patients with treatment failure.

Dynamics of conversation of sputum among these two groups of patients has been demonstrated in the following graph. As can be seen from the graph in *Figure 8*, each month was a progressive delay of the conversation of sputum in patients with “failure” of treatment.

Figure 8: Kaplan-Meier survival curve for sputum culture conversion versus treatment outcome



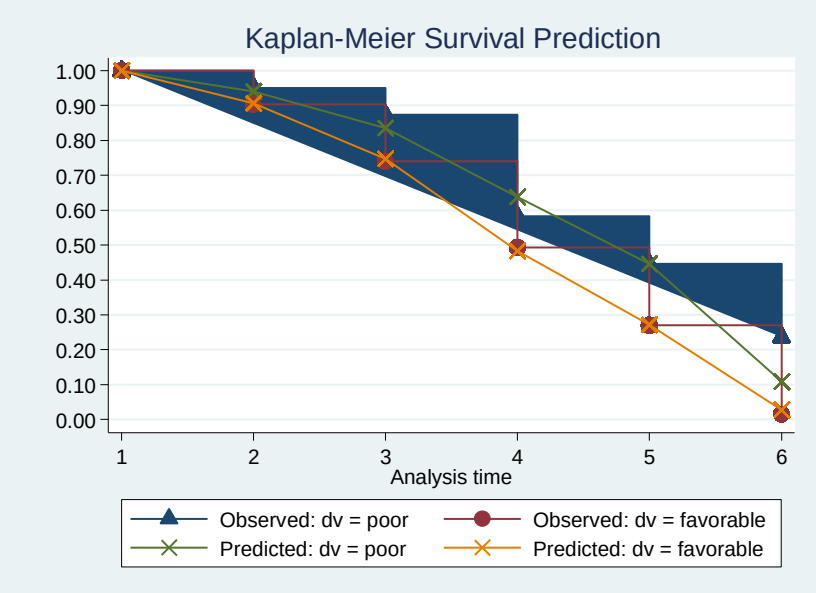
In figures it means, that 56.3% of patients with poor result in the first month and 46.8% - in the second month had positive sputum smear microscopy result, while 54.6% of patients with “treatment success” had positive sputum smear microscopy results in the first month and 29.4%- in the second month. Dynamics of sputum culture conversation among these two groups of patients were distributed as following: 36.1% of patients with “treatment success” had positive sputum culture result in the first month and 24.9% - in the second month, which was almost twice less than in patients with “poor treatment”

Similarly, 80.4% of patients with poor result in the first month and 73.3% -in the second month had positive sputum culture result.

Generated and presented in *Figure 8* Kaplan-Meier's survival curve gave dynamics of culture conversion over six months for patients of both groups (with "failure treatment" and "success"). It was clear, that starting from the second month of treatment the proportion of patients with sputum culture conversion dropped to 91% for patients with "treatment success" and to about 95% for patients with poor result In the third month it dropped to 73% for patients with "treatment success" and to 88% for patients with poor result Finally, to the sixth month the percentages of sputum culture conversion significantly decreased in both groups, however, for patients with "treatment failure" it decreased up to 29% and for patients with "treatment success" - to 2%.

The *Figure 9* reflected survival prediction for each groups. The graph showed, that the progress of the patients with "treatment success" was precisely predicted by the model, while the patients with "treatment failure" were not able to reach the point of culture conversion predicted by the model.

Figure 9: Kaplan-Meier survival curve prediction for sputum culture conversion versus treatment outcome



Resistance to Ofx is a significant reason impacting on efficacy of treatment. The study authentically detected that drug resistance to Ofx, observed more commonly in patients with "unfavorable treatment". It means that 14.3% of patients with poor result and 1.83% of patients with "treatment success" had resistance to Ofx. However, this fact needs to be further investigated because of no statistic meaning due to small number of cases (less than 5%).

The severity of the disease was evaluated based on a set of indicators (see description above). Comparing degree of severity according to the median of disease severity marker - 10 (with the range of 4 – 14), the study established, that one third of

patients - 28.4% (82) gained more than 11 points, while 71.6% (207) had 10 points and below Disease severity markers were also associated with treatment outcome. So, 78.5% of patients with “treatment success” had disease severity marker below 10, while just 44.9% of patients with poor result had this threshold.

Thus, patients with contacts with diseased person, less imprisonment frequency, delayed sputum conversion, bilateral destructive process in lungs, diabetes, reduced the growth index/weight (BMI), resistance to Ofx, with diseases severity markers above 10 points was significantly more frequent among the group of patients with poor result.

Medicines for anti-TB chemotherapy are characterized by significant toxic impacts led to arising different side effects in patients during the treatment, and sometimes cause lost of follow up to treatment. The study revealed as side effects of first and second line drugs hearing loss in 15.4% of patients with “treatment failure” and in 0.6% of patients with “treatment success”, hypomagnesaemia in 15.4% patients with “treatment failure” and in 1.7% of “cured” patients (*See Table 11*)

Table 11: Side effects associated with treatment

+	Patents “unfavorable treatment” (n=49)% (n)	Patients with “treatment success” (n=219) %	p value
Headache	7.7 (4)	11.6 (25)	0.671
Dizziness	0.00	8.1 (18)	0.286
Seizures	0.00	0.6 (1)	0.783
Peripheral neuropathy	0.00	1.7 (4)	0.631
Hearing loss	15.4 (8)	0.6 (1)	**0.000**
Psychotic symptoms	23.1 (11)	16.8 (37)	0.561
Depression	0.00	1.2 (3)	0.697
Nausea	0.00	17.3 (38)	0.101
Vomiting	0.00	3.5 (8)	0.495
Diarrhea	0.00	4.1 (9)	0.460
Abdominal pain	0.00	8.7 (19)	0.268
Skin rash	0.00	2.3 (5)	0.579
Arthralgia	15.4 (8)	15.0 (33)	0.972
Allergy	0.00	1.2 (3)	0.697
Hepatitis (s.e.)	38.5 (19)	26.6 (58)	0.355
Hypomagnesaemia	15.4 (8)	1.7 (4)	**0.003**
Sleeplessness	0.00	3.5 (8)	0.495

*Variables with bold highlight are included in multivariate analysis.
* Highlighted with yellow are not included in multivariate analysis as assumption having 5% at least in each cell was not met. Even if we include them statistical software automatically omitted them.

The rest of the factors, including age, marital status, self-treatment, HIV, hepatitis, drug abusing, tobacco use, and number of resistant drugs, and side effects such as headache, peripheral neuropathy, psychotic symptoms, depression, hypothyroidism, vomiting, diarrhea, abdominal pain, skin rash, arthralgia, allergy,

hepatitis, and sleeplessness do not show significant association with treatment outcome , are not

4.2 What are the predictors for “treatment success” of patients with MDR TB?

As it was mentioned above, all variables with p level 0.25 and below were included in multivariate logistic regression. As the *Table 12* shows, three risk factors “BMI at start”, “cavity in both sides” and “positive culture result 2nd month“ were significantly (p<0.05) associated with treatment outcome.

According to multivariate logistic regression outcomes, BMI (below 18.5) at start of treatment was risk factor for treatment with OR=0.46 (95% CI 0.23-.99). In other words, patients who had BMI lower than 18.5 points are 54% less likely having faorable treatment outcome.

The result of multivariate analysis also revealed that bilateral destruction in lungs was also risk factor with OR=0.35 (95% CI 0.16-0.75), means that patient with bilateral destructive processes in lungs had 0.1 times more chance to have failure of treatment than patients with no cavities or with unilateral cavities. By other words, patients who had cavities in both lungs were 65% less likely to have favorable treatment outcome.

Other revealed risk factors was positive sputum culture result in the second month with OR =0,18 (95% CI 0.08-0.39), means that patient with positive culture result in the second month 0.18 times less likely would have favorable treatment outcome. This means patients who had positive sputum culture result in the second month were 82% less likely to have favorable treatment outcome.

Table 12: Factors associated with treatment outcome in a multivariate logistic regression (n=239)

Risk factors	OR	95% CI	p value
Total number of imprisonment (below 3 = 0)	2.62	0.82-8.39	0.105
BMI at start (above 18.6=0)	**0.46**	**0.23-0.99**	**0.046**
Cavity in both sides	**0.35**	**0.16-0.75**	**0.007**
Positive smear result before the treatment	1.11	0.32-3.76	0.867
Positive smear result 1st month	1.21	0.48-3.04	0.683
Positive culture result 1st month	0.94	0.30-2.96	0.921
Positive smear result 2nd month	1.30	0.50-3.36	0.594
Positive culture result 2nd month	**0.18**	**0.08-0.39**	**0.000**
Disease severity markers (below 10 = 0)	0.52	0.22-1.23	0.137

Thus, multivariate analysis confirmed that BMI at start of treatment, positive sputum culture test in the second month of treatment and bilateral cavities in lungs are independent predictors of treatment failure.

5. Conclusion

- Our study intended to revealed association between co-infections (HIV, hepatitis B and C) and MDR-TB treatment outcomes. It is known that HIV is one of the influential factors on MDR TB treatment. But this dependency can be slightly manifested or even be not obvious at early stage of HIV or under ART. Our analyses did not give us markedly proof of its impact on MDR-TB poor outcomes. Fortunately, this problem is irrelevant in Azerbaijan, because of low HIV prevalence. So, this association may be investigated further.
- Hepatitis B or C or both co-infections did not affect on the results of treatment of MDR-TB patients. This is a valuable finding because such fact had never been reported. Perhaps, it has become possible due to the unique situation in prison sector of Azerbaijan - a high prevalence of carriers of the hepatitis B and C virus – over 60%!
- Univariate analysis revealed the following risk factors, such as total number of imprisonment less than three, contact with MDR-TB patient, diabetes, low BMI at start, bilateral cavities in lungs, positive sputum culture result in second month of treatment, resistance to Ofx, hearing loss, hypomagnesaemia, disease severity markers, influenced on MDR –TB treatment outcome,.
- Multivariate logistic regression confirmed the weight of bilateral destructive process in lungs and delaying of sputum conversion in second month of treatment as predictors of MDR-TB treatment failure.
- Bilateral cavities with massive bacterial loading are obvious evidence of neglected, poor treated, late diagnosed TB cases.
- Improvement of MDR-TB treatment outcome should evolve special care of advanced TB cases with extensive damaging of lungs and massive bacilli loading.
- In our study disease severity markers has not been revealed as a independent risk factors. Existed disease severity markers are not precise to be used as a predictor. It needs to be revised and extended with including in the all risk factors found in our study.

6. Recommendations

- Addressing to issue of patients with extensive disease and massive bacilloloading, i.e early detection patients and combined approach to treat them with chemotherapy as well as surgery in accordance with revealed risk factors
- Majority of MDR-TB patients are infected for a long time, late diagnosed, treated previously. For such category of advanced patient including surgical approach in treatment is an optimal way of improving treatment outcome.

7. Reference list

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