INT J TUBERC LUNG DIS 10(4):402–408

Treatment outcomes in an integrated civilian and prison MDR-TB treatment program in Russia

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SUMMARY

SETTING: Multidrug-resistant tuberculosis (MDR-TB) is a major problem in countries of the former Soviet Union in both the civilian and prison sectors.

OBJECTIVE: To evaluate outcomes of the MDR-TB treatment program (DOTS-Plus) in Tomsk, Russia.

DESIGN: Retrospective case series of all patients enrolled in this program between 10 September 2000 and 10 September 2002. The program involves both the civilian and penitentiary TB services in Tomsk. Poor treatment outcome was defined as death, default and treatment failure.

RESULTS: Among the 244 patients who received treatment, 77% were cured, 5% died, 7% failed, and 12% defaulted. In a multivariable analysis, alcohol consumption during treatment and the presence of both cavitary and bilateral disease were found to be the strongest predictors of poor treatment outcome.

CONCLUSIONS: The integration of civilian and penitentiary TB services in the Tomsk MDR-TB treatment program has resulted in high cure rates and low rates of default. However, alcohol use among patients with MDR-TB is associated with poor treatment outcomes. Better understanding and programmatic alcohol interventions are needed if large-scale treatment of MDR-TB is to be successful in areas with high rates of alcohol use disorders.

KEY WORDS: multidrug-resistant tuberculosis; DOTS-Plus; Russia; alcohol

THE EMERGENCE of multidrug-resistant (MDR) strains of *Mycobacterium tuberculosis* has had a substantial impact on tuberculosis (TB) epidemiology in the Russian Federation since the collapse of the Soviet Union (SU) in 1991.[1] The decline of the Russian public health infrastructure, and in particular TB services, has led to a resurgence of TB, which had previously been well controlled.[2] The prevalence in Russia of MDR-TB—defined as strains resistant to at least isoniazid (INH) and rifampin (RMP)—is among the highest in the world, reported to be as high as 13.7% among new (primary) cases and 25.9% among previously treated cases in certain areas of Russia.[3] The penitentiary system has been a major source of MDR-TB transmission in the Russian Federation, with rates of primary MDR as high as 22.6%.[4,5] Rates of MDR-TB are also high in the civilian sector.[6] DOTS regimens in specific regions of Russia have yielded poor treatment results, in large part due to drug resistance.[7–9]

Recognizing the inadequacy of DOTS alone in controlling the rise of MDR-TB and TB overall, numerous sites in Russia and the former SU have adopted DOTS-Plus, an MDR-TB treatment strategy endorsed by the World Health Organization (WHO) for lower- and middle-income countries.[10] This strategy builds upon the foundation of DOTS, but also provides a framework for MDR-TB treatment using second-line drugs based on individual or regional drug susceptibility data.

The Tomsk Oblast in Western Siberia exemplifies the MDR-TB dynamics observed in many parts of Russia. From 1998 to 2002, rates of MDR-TB rose from 6.5% to 13.7% among newly detected cases, and from 26.7% to 43.6% among previously treated cases.[11] Approximately 36% (36.2%) of TB isolates

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Article submitted 21 July 2005. Final version accepted 1 November 2005.

from drug-resistant patients in Tomsk are resistant to at least three drugs.[11] Despite the implementation of DOTS in 1995 for newly diagnosed smear-positive patients in 1995 and 1996, only 62% achieved successful outcomes.[9] Not surprisingly, MDR-TB patients had worse treatment outcomes than patients with drug-susceptible TB, with culture conversion achieved in only 40% of those with MDR-TB after 6 months of DOTS.[9]

In 2000, a collaborative DOTS-Plus program was initiated to provide MDR-TB therapy within the existing Tomsk TB Program infrastructure. Participants of this international effort included the Tomsk Oblast TB Services (TOTBS), the Tomsk Oblast Penitentiary System, Russian Federation Ministries of Health and Justice, the Open Society Institute, Medical Emergency Relief International, the Public Health Research Institute, Partners In Health, the Siberian State Medical University, and the Massachusetts State Laboratory Institute (MSLI). We describe here the first MDR-TB treatment program to provide individualized therapy to both prison and civilian populations.

STUDY POPULATION AND METHODS

Study patients

The Tomsk Oblast is located in western Siberia and comprises approximately 1 068 000 inhabitants in an area roughly the size of Poland. Half of the population lives in the capital city of Tomsk, and the remainder lives in remote rural villages throughout the oblast, which are often inaccessible for parts of the year. We studied a retrospective cohort of all 244 patients consecutively enrolled to receive DOTS-Plus treatment between 10 September 2000 and 10 September 2002. Patients were enrolled based on the following eligibility: 1) active TB as evidenced by positive culture at the time of enrollment or by previous treatment failure with clinical evidence of active disease; 2) documented MDR-TB (in 243 cases) or suspected MDR-TB based on a history of previous treatment failures (in the remaining one case); and 3) willingness to receive DOTS-Plus treatment.

Bacteriologic studies and drug susceptibility testing

Smear microscopy and culture on Löwenstein-Jensen media are performed according to international standards in local mycobacteriology laboratories. For all patients, isolates obtained prior to starting DOTS-Plus are sent for susceptibility testing against at least five drugs (INH 1 μg/ml, RMP 40 μg/ml, ethambutol [EMB] 5 μg/ml, streptomycin [SM] 10 μg/ml, and kanamycin [KM] 30 μg/ml) in the Tomsk referral laboratory, using the absolute concentration method.[12] In addition, most samples are sent to the MSLI for drug susceptibility testing (DST) of the following: INH 0.2, 1 and 5 μg/ml, RMP 1 μg/ml, pyrazinamide (PZA) 100 μg/ml, EMB 5 μg/ml, SM 2 and 10 μg/ml, KM 5 μg/ml, capreomycin 30 μg/ml, ethionamide (ETH) 30 and 50 μg/ml, cycloserine 30 μg/ml, para-aminosalicylic acid 1 μg/ml, amikacin 6 μg/ml, levofloxacin 1 μg/ml, ofloxacin 2 μg/ml and ciprofloxacin 2 μg/ml. At the MSLI, the proportion method[12] on 7H10 agar plates is used for testing all drugs except for PZA, for which BACTEC is performed.[13]

Regimen design and patient management

Individualized MDR-TB regimens are designed based on the resistance profile of each individual's isolate according to guidelines described elsewhere.[14] Whenever possible, regimens consist of at least five drugs to which the patient's isolate is susceptible. All doses are directly observed. In addition to monthly sputum smear and culture, chest radiographs (CXRs) are performed at least every 3 months and computed tomography scans when needed. All patients are tested at baseline for human immunodeficiency virus (HIV) using enzyme-linked immunosorbent assay (ELISA). TB physicians routinely assess all patients initiating treatment for possible alcohol and/or substance use disorders. While Russian physicians generally base these diagnoses on International Classification of Diseases 10 (ICD-10) classifications, no standard diagnostic tool is used. Patients are routinely hospitalized during the intensive phase (the duration of injectable therapy). The continuation phase (after discontinuation of the injectable) is usually administered on an ambulatory basis, using a community-based approach to provide flexible directly observed therapy and adherence incentives and enablers.[15] However, some individuals receive the continuation phase as in-patients, in particular if an underlying condition, such as psychiatric disorder, alcoholism or homelessness, precludes discharge.

Ambulatory care is provided at a day hospital, several out-patient TB clinics, and rural health posts staffed by mid-level health providers. Patient care is coordinated closely between the civilian and prison sectors to minimize treatment disruption for patients undergoing transfer. Supplementary nutritional support is also provided to prisoners and in-patients receiving MDR-TB treatment. Monthly food packages and/or free meals are given to fully adherent patients during treatment in the ambulatory sector. Adverse reactions are managed aggressively, making every attempt to avoid discontinuation of necessary TB drugs. The occurrence of adverse reactions has been described elsewhere; notably, discontinuation of a drug due to adverse reactions occurred rarely, compared with other DOTS-Plus programs.[16] Treatment is continued for at least 12 months prior to assessing for treatment failure, and generally at least 18 months prior to considering cure.

Data collection and analysis

Data were collected retrospectively by chart review using standardized forms, entered into a DOTS-Plus Electronic Medical Record, which used a Microsoft SQL server 2000 (Microsoft Corp, Redmond, WA)

Table 1 Baseline characteristics of 244 patients enrolled in the DOTS-Plus program in Tomsk between 10 September 2000 and 10 September 2002

Characteristic (*N*, if not 244)	*n* (%)	Median (range)
Sex		
Male	211 (86.5)	
Female	33 (13.5)	
Age, years		32.3 (16–65)
Sector		
Prison	110 (45.1)	
Civilian	134 (54.9)	
Civil status (240)		
Married	91 (37.9)	
Single	127 (52.9)	
Divorced	19 (7.9)	
Widowed	3 (1.3)	
Employed (241)	41 (17.0)	
Disability (238)	99 (41.6)	
Homeless (242)	8 (3.3)	
Previous treatments (239)		2.0 (1–6)
Years with TB prior to DOTS-Plus (243)		3.3 (0.1–28.3)
TB contact (180)	121 (67.2)	
Health care worker (241)	6 (2.5)	
Previous or present incarceration	155 (64.3)	
Low body mass index	102 (41.8)	
Body mass index		20.5 (13.5–32.0)
Comorbid condition (any)	102 (41.8)	
HIV	0	
Hepatitis and/or abnormal baseline liver function tests	44 (18.0)	
Chronic renal insufficiency	3 (1.2)	
Diabetes mellitus	9 (3.7)	
Cardiovascular disease	13 (5.4)	
Gastritis or history of gastric ulcer	34 (14.2)	
Seizure disorder	7 (2.9)	
Baseline psychiatric disorder	14 (5.8)	
Substance abuse/dependence (any)	122 (50.0)	
Alcohol abuse/dependence	86 (35.3)	
Illicit drug abuse/dependence	43 (17.6)	
Alcohol use during treatment	77 (31.6)	
Illicit drug use during treatment	13 (5.33)	
Tobacco use	215 (88.1)	
Previous surgery for TB (242)	24 (9.9)	
Extra-pulmonary TB (192)	20 (10.4)	
Severe baseline clinical status*	142 (58.2)	
Both cavitary and bilateral disease (240)	159 (66.3)	
Culture-positive at treatment initiation	230 (94.3)	
Drugs to which *M. tuberculosis* strain was resistant (243)†		
All drugs		5 (3–9)
First-line		4 (3–5)
Second-line		1 (0–4)

* Respiratory insufficiency, hemoptysis, and/or high burden smear at baseline.
†First-line drugs: isoniazid, rifampin, ethambutol, pyrazinamide, streptomycin; second-line drugs: kanamycin, capreomycin, ciprofloxacin, fluoroquinolone, cycloserine, ethionamide.
TB = tuberculosis; HIV = human immunodeficiency virus.

and exported into an Access 2000 database (Microsoft Corp). Interim and final treatment outcome definitions by the MDR-TB Working Group were used for this study.[17] Poor treatment outcome was defined as default, failure, or death of any cause during TB treatment. Analysis was conducted using SAS Version 9.1 (SAS Institute, Inc, Cary, NC). Univariate and multiple logistic regression models were used to generate effect estimates of the association between patient characteristics and poor treatment outcome. Variables included in univariate analysis were chosen based on existing scientific literature and the observations of Tomsk physicians, who identified common characteristics felt to be linked to poor treatment outcomes. Non-collinear variables associated with poor treatment outcome in the univariate analysis ($P < 0.05$) were entered into the multivariable analysis. Variables included in the multivariable analysis were assessed for effect modification.

RESULTS

Baseline patient characteristics

As shown in Table 1, this was a young, predominantly male cohort of 244 individuals. Enrollment was divided roughly equally between prison and civilian sectors. Among those initiating treatment in the civilian sector, 98 (73.1%) started treatment in the inpatient hospital, while the remainder started in the day hospital. Most patients were unemployed, and approximately 42% received disability support. Among comorbid conditions, liver dysfunction and gastritis were the most common. Alcohol abuse/dependence was diagnosed by the treating physician in 35.3% of patients; among these, alcohol use during TB treatment was documented in 61.6%, and 43.2% had baseline hepatic dysfunction. As shown in the Figure, most patients were resistant to all first-line drugs. Among the second-line drugs, resistance to KM (47.7%) and ETH (44.0%) was common, while resistance to fluoroquinolones was relatively rare (6.2%).

Characteristics of MDR-TB treatment

The median duration of the intensive phase was 8.6 months, with a range of zero to 27.5 months. For those initiating treatment in the TB hospital, transfer

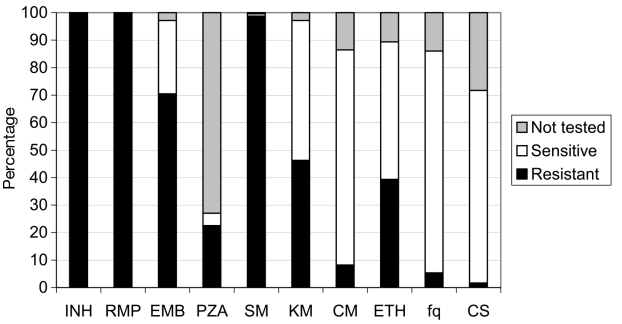

Figure Resistance patterns among 243 patients. INH = isoniazid; RMP = rifampin; EMB = ethambutol; PZA = pyrazinamide; SM = streptomycin; KM = kanamycin; CM = capreomycin; ETH = ethionamide; fq = fluoroquinolone; CS = cycloserine.

Table 2 Characteristics of patients and DOTS-Plus treatments ($N = 244$)

Characteristic (N, if not 244)	Frequency (%)	Median (range)
Patients who received surgery, n	24 (9.8)	
Thoracoplasty	4	
Segmental resection (⩾1)	5	
Lobectomy	14	
Pneumonectomy	1	
Percentage of missed doses*		5% (0–45%)
Time to culture conversion, months ($n = 218$)		2 (1–18)
Duration of therapy, months		
All patients		18.5 (1.0–42.4)
Cures		18.8 (16.1–42.4)
Failures		18.9 (10.1–28.1)
Deaths		10.9 (1.8–22.9)
Defaults		9.2 (1.0–15.7)

* Defined as the percentage of doses among all prescribed doses missed throughout DOTS-Plus treatment, as recorded on the treatment administration forms.

to out-patient services occurred after a median of 7.9 months. A total of 45 individuals (33.6% of the civilian sector patients) were eventually transferred to raions (regions within an oblast) outside of Tomsk, predominantly to rural villages. Twenty-three prisoners (20.9%) were transferred to the civilian sector after a median of 12.6 months; two defaulted at the time of release, while the remaining 21 patients (91.3%) successfully continued treatment. Another three patients were incarcerated during their treatment and continued treatment in prison. As shown in Table 2, among the 230 patients who had positive baseline cultures, 218 (94.8%) achieved culture conversion after a median of 2 months of therapy.

Outcomes and predictors

Cure was achieved in 77.0% of the cohort; 4.9% died, 6.6% failed treatment, and 11.5% defaulted. There were no transfers. Among the 12 patients who died during TB treatment, four died due to TB. Causes of the non-TB deaths were: accidents (2); myocardial infarction (2); homicide (1); suicide (1); and alcohol-related (2).

A univariate analysis (Table 3) identified several variables associated with poor treatment outcome: initiation of treatment in the civilian sector, alcohol abuse/dependence, reported alcohol use during TB treatment, presence of both cavitary and bilateral disease, severe baseline clinical status, and percentage of missed doses. No effect modification was found among these variables. Table 4 summarizes the multivariable analysis, which included the following non-collinear variables: sector upon treatment initiation, bilateral and cavitary disease, severe baseline clinical status, alcohol use during treatment, and percentage of missed

Table 3 Factors associated with poor outcome ($N = 244$)

Characteristic	Patients with favorable outcome ($n = 188$) %	Patients with poor outcome ($n = 56$) %	P value
Male sex	85.1	91.1	0.37
Age by quartiles			0.12
<26	29.3	19.6	
⩾26 and <32	23.9	16.1	
⩾32 and <43	22.9	35.7	
⩾43	23.9	28.6	
Treatment started in prison	48.9	32.1	0.03
Number of previous treatments (> median)	41.9	47.3	0.48
Low body mass index	41.5	42.9	0.86
Comorbid condition	27.7	30.4	0.69
Extra-pulmonary tuberculosis	8.8	15.9	0.26
Alcohol abuse/dependence	31.9	46.4	0.046
Illicit drug abuse/dependence	16.5	21.4	0.39
Alcohol use during treatment	25.5	51.8	0.0002
Illicit drug use during treatment	3.7	10.7	0.08
Severe baseline clinical status	53.7	73.2	0.009
Both cavitary and bilateral disease	61.1	83.6	0.002
Baseline resistance to > median number of drugs	37.7	30.4	0.32
Quinolone resistance	5.7	7.7	0.74
Percentage of missed doses			0.04
<2.0%	25.0	8.9	
⩾2.0% and <5.0%	27.1	30.4	
⩾5.0% and <11.0%	25.5	25.0	
⩾11.0%	22.3	35.7	
Surgery during DOTS-Plus	11.7	12.5	0.87

Table 4 Factors associated with poor outcomes in a multivariable analysis ($n = 244$)

Characteristic	Adjusted OR (95%CI)	*P* value
Treatment started in prison	0.86 (0.35–2.13)	0.75
Both cavitary and bilateral disease	2.58 (1.15–5.79)	0.02
Severe baseline clinical status	1.22 (0.49–3.02)	0.66
Alcohol use during treatment	2.25 (1.05–4.83)	0.04
Percentage of missed doses	1.34 (0.98–1.82)	0.06

OR = odds ratio; CI = confidence interval.

doses. Alcohol use during treatment (odds ratio [OR] 2.25, 95% confidence interval [CI] 1.05–4.83) and bilateral and cavitary disease (OR 2.58, 95%CI 1.15–5.79) were found to be significantly associated with poor treatment outcome.

DISCUSSION

As with other sites with high rates of MDR-TB,[18–20] the most vulnerable portion of society is disproportionately affected. Our cohort in Tomsk is comprised largely of incarcerated, homeless and unemployed individuals, and those suffering from substance use and/or dependency. Nonetheless, the results of this study demonstrate cure and default rates that are comparable to those achieved in other programs, despite the vulnerable socio-economic status and high rate of substance abuse in our cohort.[21–25]

This study is limited by several features. Because of the retrospective nature of this study, we were unable to identify individuals with alcohol and/or substance use disorders in a systematic, prospective manner. TB physicians evaluated patients for alcohol and/or substance use disorders without using a standardized, validated instrument. It is therefore possible that only the most severe cases of alcohol and drug disorders were identified. Indeed, the rate of substance dependence/abuse in this cohort is lower than that observed in other Russian TB cohorts.[6,9,26] In addition, there may have been a bias toward documenting alcohol consumption among those individuals who were doing poorly on TB treatment. However, the prevalence of alcohol use during treatment report here is, if anything, an underestimate of the true scope of the problem.

Furthermore, the population treated in this cohort may not reflect the overall MDR-TB population in Tomsk; these patients represent the earliest cohort to be enrolled in this program and may have different clinical and social characteristics compared with patients who were enrolled later. The authors have observed that the patients enrolled into the Tomsk MDR-TB program subsequent to this cohort tend to have more severe clinical manifestations of their disease and deeper psychosocial and addiction challenges.

Despite these limitations, several important lessons can be drawn from these results. While the association between alcohol use disorders and poor TB treatment outcomes has been described previously,[26–29] this is the first study to demonstrate the association between alcohol use and poor outcome specifically among MDR-TB patients. We feel that this is an important finding, because alcohol and substance use may pose substantial challenges in MDR-TB treatment throughout Russia and the former SU as DOTS-Plus programs are scaled up. Use of standardized diagnostic instruments and evidenced-based alcohol interventions in this population could improve TB outcomes. Measures are currently underway in Tomsk to improve care for alcohol use disorders among TB patients. Importantly, despite the effect of alcohol use on treatment outcome, cure was still achieved in the majority of individuals (62.3%) who were consuming alcohol; thus, we argue that inclusion of patients with substance use disorders in MDR-TB treatment programs is not only feasible, but also necessary.

Another important finding in this study is the low rate of non-adherence in this cohort. Non-adherence was minimized to a median of 5% missed doses throughout DOTS-Plus treatment by using incentives and enablers. The provision of food and transportation incentives as well as increased social support to patients receiving TB treatment is supported by the WHO,[30] and has been shown to improve outcomes in Russia and elsewhere, particularly through improved adherence to treatment.[31,32] Here, this strategy has been incorporated into the DOTS-Plus model, similar to the approach that was taken in the DOTS-Plus pilot program in Lima, Peru.[23,33]

These results demonstrate the feasibility of carrying out a comprehensive program to treat both civilian and prison populations in both urban and rural settings covering extensive geographic territory. As Russia now moves to scale up MDR-TB treatment to the national level, the success of this program may serve as a model for implementation of similar programs elsewhere in Russia and parts of the former SU.

Acknowledgements

Funding for medications and patient care was provided by the Bill & Melinda Gates Foundation and the Open Society Institute. Funding for physician and health care worker training was provided by the Eli Lilly foundation. The authors would like to recognize the contributions of S Atwood, D Balbuena, G Fitzmaurice, J Furin, G Jones, A Judd, M Murray, E Nardell, O Ponomarenko, O Sirotkina, A Sloutsky, L Sloutsky, and J Kim.

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RÉSUMÉ

CONTEXTE : La tuberculose à germes multirésistants (TB-MR) est un problème majeur dans les pays de l'ancienne Union Soviétique, à la fois dans le secteur civil et celui des prisons.

OBJECTIF : Evaluer les résultats du programme de traitement des TB-MR (DOTS-Plus) à Tomsk, Russie.

SCHÉMA : Séries rétrospectives des cas de tous les patients enrôlés dans ce programme entre le 10 septembre 2000 et le 10 septembre 2002. Le programme implique à la fois les services de TB civils et pénitentiaires de Tomsk. On a décrit comme piètres résultats du traitement le décès, l'abandon ou l'échec du traitement.

RÉSULTATS : Sur 244 patients traités, il y a eu 77% de guérisons, 5% de décès, 7% d'échecs et 12% d'abandons. A l'analyse multivariée, les facteurs prédictifs les plus marqués d'un piètre résultat du traitement ont été la consommation d'alcool au cours du traitement et la présence de TB à la fois cavitaires et bilatérales.

CONCLUSIONS : Dans le programme de traitement de la TB-MR de Tomsk, l'intégration des services TB civils et pénitentiaires a entraîné des taux élevés de guérison et de faibles taux d'abandon. Toutefois, la consommation d'alcool par les patients atteints de TB-MR est associée aux piètres résultats du traitement. Une meilleure compréhension et des interventions du programme en matière d'alcool sont nécessaires si l'on veut qu'un traitement de la TB-MR sur une large échelle soit couronné de succès dans les zones où les taux d'affections liées à l'alcool sont élevés.

RESUMEN

MARCO DE REFERENCIA : La tuberculosis multidrogorresistente (TB-MDR) constituye un grave problema en los países de la antigua Unión Soviética, para la población del sector civil y del sector penitenciario.

OBJETIVO : Evaluar los resultados del programa de tratamiento de la TB-MDR con la estrategia DOTS-Plus en Tomsk, República de Rusia.

MÉTODO : Se estudiaron retrospectivamente todos los pacientes inscritos en este programa entre el 10 de septiembre de 2000 y el 10 de septiembre de 2002. El programa incluyó los programas de TB en la población civil y en la población carcelaria de Tomsk. Se definió como desenlace desfavorable la muerte, el abandono y el fracaso del tratamiento.

RESULTADOS : De los 244 pacientes que recibieron tratamiento, 77% alcanzaron la curación, 5% fallecieron, en el 7% fracasó el tratamiento y 12% lo abandonaron. En el análisis multifactorial de regresión logística se encontró que el consumo de alcohol durante el tratamiento y la presencia bilateral de cavernas fueron los principales factores pronósticos independientes del desenlace desfavorable del tratamiento.

ONCLUSIONES : La integración de los servicios de TB de la población civil y carcelaria al programa de tratamiento de la TB-MDR ha procurado altas tasas de curación y bajas tasas de abandono. Sin embargo, el consumo de alcohol de los pacientes con TB-MDR se correlaciona con desenlaces terapéuticos desfavorables. Con el fin de lograr un tratamiento exitoso de la TB-MDR en gran escala, se precisan una mejor comprensión e intervenciones programadas con el objeto de combatir el consumo de alcohol, en las zonas con altas tasas de morbilidad por alcoholismo.