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## Alcohol and drug use disorders, HIV status and drug resistance in a sample of Russian TB patients

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### SUMMARY

**SETTING:** Alcohol use, tuberculosis (TB) drug resistance and human immunodeficiency virus (HIV) risk behavior are of increasing concern in Russian TB patients.

**DESIGN:** A prevalence study of alcohol use and HIV risk behavior was conducted in a sample of 200 adult men and women admitted to TB hospitals in St Petersburg and Ivanovo, Russia.

**RESULTS:** Of the subjects, 72% were men. The mean age was 41. Active TB was diagnosed using a combination of chest X-ray, sputum smears and sputum cultures. Sixty-two per cent met DSM-IV criteria for current alcohol abuse or dependence. Drug use was uncommon, with only two patients reporting recent intravenous heroin use. There was one case of HIV infection. The mean total risk assessment battery score was 3.4. Depression was present in 60% of the sample, with 17% severely depressed. Alcohol abuse/dependence was associated with an eight-fold increase in drug resistance (OR 8.58; 95% CI 2.09-35.32). Patients with relapsing or chronic TB were more likely to meet the criteria for alcohol abuse/dependence (OR 2.56; 95% CI 1.0-6.54).

**CONCLUSION:** Alcohol use disorders are common in patients being treated for active TB, and are associated with significant morbidity. Additional surveys are needed to examine the relationship between alcohol use disorders and anti-tuberculosis drug resistance.

**CONTEXTE:** Chez les patients tuberculeux russes, l'utilisation d'alcool, la résistance aux médicaments antituberculeux et un comportement à risque pour le virus de l'immunodéficience humaine (VIH) sont des sujets croissants d'inquiétude.

**SCHÉMA:** Une étude de prévalence de l'utilisation d'alcool et du comportement à risque pour le VIH a été menée sur un échantillon de 200 hommes et femmes adultes, admis dans des hôpitaux pour la tuberculose (TB) de Saint-Petersbourg et d'Ivanovo en Russie.

**RÉSULTATS:** Il y avait 72% d'hommes dans l'échantillon. L'âge moyen est de 41 ans. On a diagnostiqué la TB active par l'emploi d'une combinaison du cliché thoracique, de la bacilloscopie et des cultures d'expectoration. Chez 62% des patients, les critères DSM-IV pour utilisation courante d'alcool ou pour dépendance étaient présents. L'utilisation de drogues est inhabituelle: deux patients seulement ont signalé une utilisation récente de l'héroïne par voie intraveineuse. Il n'y avait qu'un seul cas d'infection VIH. Le score total moyen de la batterie d'évaluation des risques a été de 3,4. Il y avait de la dépression chez 60% de l'échantillon, dont 17% étaient en dépression sévère. L'utilisation ou la dépendance à l'égard de l'alcool étaient associées avec une multiplication par huit

de la résistance aux médicaments (OR 8,58 ; IC95% 2,09-35,32). Les patients atteints de rechute de TB ou de TB chronique sont plus susceptibles de répondre aux critères d'abus ou de dépendance de l'alcool (OR 2,56; IC95% 1,0-6,54).

**CONCLUSION:** Les maladies liées à l'utilisation d'alcool sont fréquentes chez les patients traités pour TB active et sont associées à une morbidité significative. Des enquêtes complémentaires sont nécessaires pour examiner les relations entre les maladies liées à l'utilisation d'alcool et la résistance à l'égard des médicaments antituberculeux.

**MARCO DE REFERENCIA:** El consumo de alcohol, la tuberculosis (TB) farmacorresistente y los comportamientos de riesgo para la infección por el virus de la inmunodeficiencia humana (VIH) constituyen una preocupación creciente en los pacientes con TB en la Federación de Rusia.

**MÉTODOS:** Se llevó a cabo un estudio de prevalencia del consumo de alcohol y del comportamiento de riesgo para la infección por el VIH en una muestra de 200 adultos, hombres y mujeres, ingresados por TB en dos hospitales de San Petersburgo e Ivanovo en la Federación de Rusia.

**RESULTADOS:** El 72% de los individuos fueron de sexo masculino. La media de la edad fue 41 años. El diagnóstico de TB activa se estableció mediante una combinación de criterios que incluyeron la radiografía de tórax y la baciloscopia y cultivo del esputo. El 62% de los individuos cumplió con los criterios diagnósticos de alcoholismo actual o dependencia al alcohol de la nomenclatura del DSM-IV. El consumo de drogas fue poco frecuente, pues sólo dos pacientes comunicaron uso intravenoso reciente de heroína. Se observó un caso de infección por el VIH. La media total obtenida con el cuestionario auto-administrado para evaluación de los comportamientos de riesgo para sida (*risk assessment battery*) fue 3,4. El 60% de los pacientes presentaron depresión y en 17% la depresión fue grave. El alcoholismo y la dependencia al alcohol se asociaron con una frecuencia ocho veces mayor de farmacorresistencia (OR 8,58; IC95% 2,09-35,32). Los pacientes con TB crónica o recaída tuvieron mayor probabilidad de cumplir con los criterios para alcoholismo y dependencia al alcohol (OR 2,56; IC95% 1,0-6,54).

**CONCLUSIÓN:** Los trastornos por consumo de alcohol son frecuentes en pacientes tratados por TB activa y se asocian con una morbilidad considerable. Se precisan estudios adicionales para evaluar la relación entre estos trastornos y la resistencia a los medicamentos antituberculosos.

## Keywords

tuberculosis; TB; HIV; drug resistance; Russia

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TUBERCULOSIS (TB) kills more people worldwide than any other infectious disease. Russia is among a growing number of countries that have experienced a resurgence of TB. The World Health Organization (WHO) rates Russia among the 22 high-burden countries based on TB incidence and the absolute number of new cases. Between 1988 and 1999, the death rate due to TB in Russia increased from 7.7 to 20 per 100 000 population. From 1990 to 2002, the notification rate of new TB cases increased from 34 to 87/100 000.<sup>1</sup> Of additional concern is the rising rate of multidrug-resistant TB (MDR-TB, defined as resistance to at least isoniazid [INH] and rifampicin [RMP]). Estimates for 2003 suggest that 8-12% of all new TB cases in Russia were resistant to two or more anti-tuberculosis drugs.<sup>2,3</sup>

There are a number of reasons for the resurgence of TB, including reductions in funding for TB control programs, high unemployment rates, reductions in individual income, nutritional issues dissolution of social support systems and high rates of alcoholism.<sup>4</sup> The WHO, the US Centers for Disease Control and Prevention (CDC) and other members of the world community have developed tools such as directly observed treatment (DOT) and the DOTS strategy in response to the emergence of MDR-TB and associated infections such as the human

immunodeficiency virus (HIV). DOTS is a combination of technical and managerial components that ensures the availability of a diagnostic and treatment network that is easily accessible to the population. DOT is a treatment strategy in which a specifically trained health care worker observes patients swallowing their anti-tuberculosis drugs.<sup>5</sup> These initiatives have increased treatment adherence and completion rates in several countries.<sup>1</sup>

The WHO estimates that up to 30% of persons with active TB in Russia default from treatment.<sup>6</sup> Default is defined by the WHO as 'persons whose TB treatment is interrupted for 2 or more consecutive months'.<sup>1</sup> Many patients who fail to complete treatment come from marginalized groups such as ex-prisoners and alcoholics. A 2003 survey of TB patients in seven Russian oblasts found that 44% abused alcohol 9.5% were ex-prisoners and 21% were employed. TB patients who abused alcohol had a seven-fold increased risk of not completing their TB treatment (odds ratio [OR] 7.1, 95% confidence interval [CI] 3.1-17.3).<sup>6</sup>

The purpose of this report is to present new information on the frequency of alcohol use and drug use disorders in patients being treated for TB and associated comorbid factors such as risk of HIV and depressive symptoms.

## METHODOLOGY

This interview-based study was conducted in 2002-2003 among a sample of 200 patients recently admitted to one of two TB hospitals for treatment of active TB. The first study site was a TB hospital in St Petersburg located in one of Russia's major teaching hospitals for infectious disease and affiliated with the St Petersburg State Pavlov Medical University. The second site was a TB hospital in Ivanovo, a city of 500,000 people, 400 km east of Moscow. This site is one of three initial WHO test sites for the DOTS strategy now being implemented throughout Russia.

The study was approved by the University of Wisconsin (UW) Health Sciences Human Subjects Committee, the Johns Hopkins Human Subject Committee in Baltimore, MD, USA, and the Pavlov Medical Academy Human Subjects Committee in St Petersburg, Russia.

All adults admitted to the two hospitals for treatment of active TB were asked to participate in the study. Subjects were approached by one of the two researchers at each of the sites and were interviewed within 1 week of admission. Refusal rates were <5%. The primary reason for non-participation was acute illness related to TB. Subjects were offered an incentive of food and personal items for their time.

The research interviews were performed on site at each TB hospital; they were conducted in Russian and took approximately 45 min to complete. The two researchers who conducted the interviews at each site were physicians trained in addiction medicine or TB. Patient information on TB was obtained from the subjects' medical records, hospital laboratories and radiological departments; both hospitals have on-site radiological and bacteriological laboratories. The diagnosis of active TB was based on abnormal chest X-ray (CXR), positive sputum smear, and other findings. Sputum specimens and cultures were collected as part of routine clinical care at both sites. Isolates were identified and characterized using standard procedures.<sup>7</sup>

Cultures and drug sensitivity testing (DST) at the St Petersburg TB Hospital were performed by laboratory technicians associated with Pavlov Medical University. Drug sensitivity was determined using minimum and maximum concentrations of nine anti-tuberculosis drugs. The laboratory was supervised by staff from the St Petersburg TB Research Institute. Isolates were periodically sent to the TB Research Institute for replication of the DST results.

The Ivanovo tuberculosis microbiological laboratory was set up and supervised by research staff for the United States-based CDC and Russian State Center for Applied Microbiology. DST against INH (1 µg), streptomycin (SM) (5 µg/ml), pyrazinamide (PZA) (30 µg/ml), ethambutol (EMB) (2 µg/ml) and RMP (20 µg/ml) was performed using the absolute concentration method on Löwenstein-Jensen media.<sup>7</sup> A quality control study was performed by the CDC in 2001.<sup>8</sup> DST concordance between the CDC and Ivanovo laboratory was performed on 31 isolates at high risk for MDR: concordance for INH was 96%, RMP 96%, SM 98% and EMB 78%.

Primary variables of interest for this study included alcohol and drug use, alcohol and drug dependence, alcohol and drug comorbid factors HIV risk behaviors and HIV status socio-demographic factors, TB diagnosis, TB severity and drug resistance. The primary measures included a 90-day follow-back for alcohol and drug use,<sup>9</sup> the addiction severity index (ASI),<sup>10</sup> a DSM-IV alcohol/drug abuse/dependence scale,<sup>11</sup> the Beck depression inventory (BDI),<sup>12</sup> and the risk assessment battery (RAB) for HIV risk behaviors.<sup>13</sup>

Alcohol use in the 90 days prior to admission to the TB hospital was assessed using a calendar follow-back procedure. The ASI assesses seven areas, including medical problems, employment, alcohol, drugs, legal, family problems, and psychological symptoms and treatment. An adjusted composite score ranging from 0 to 1.0 is calculated for each of the seven problem areas. The BDI is a 21-question self-administered questionnaire with scores ranging from 0 to 63. A score of <10 is considered within the normal range of mood states, scores of 10 to 20 suggest mild depression, and scores >20 suggest moderate to severe depression.

The RAB was primarily developed for assessment of high-risk drug users, and assesses drug injection and sexual risk behaviors for HIV. The drug risk scale includes eight questions on sharing needles, using rinsing water and visits to sites set up for illegal intravenous injections. The sexual risk scale consists of nine questions, with 18 as the highest possible score. The total RAB score combines drug injection and sexual risk behaviour for a total possible score of 40. All patients are routinely tested for HIV on admission to the two study hospitals.

Data were entered into an Access database by the research staff at Pavlov Medical University. Analyses were performed at the University of Wisconsin using SPSS software (SPSS Inc, Chicago, IL, USA). The preliminary analysis included descriptive statistics of the sample by site. *t*-tests were used to test for differences between groups as regards age, sex, employment and alcohol use disorders. Logistic regression modeling was performed to assess the relationship of alcohol use with drug resistance. The ORs were adjusted for sex and age.

## RESULTS

Two hundred adult men and women with active TB agreed to participate in the study. Table 1 compares the participants from the two sites. The mean age of the combined sample was 41.5 (range 19-79 years); 143 (72%) were males and 57 (28%) were females. Only 67 (33%) subjects had worked in the last year. One hundred and fifty-seven (78%) were new cases, defined by the WHO as “patients who have never had treatment for TB or who have taken anti-tuberculosis drugs for <1 month”.<sup>1</sup> Twenty-seven subjects (14%) had a recent relapse of TB symptoms. A relapse case was defined by the WHO as “a patient previously declared cured, but with a new episode of positive smear or culture”.<sup>1</sup> Sixteen (8%) subjects were admitted to the TB hospital with chronic TB. There were more relapsed and chronic cases at the St Petersburg site.

One hundred and thirty-six subjects (63%) had CXR evidence of pulmonary infiltration, 14 (7%) fibrosis and cavities, four (2%) caseous pneumonia, two (1%) pleural effusion only and 52 (26%) a combination of radiological findings. CXRs of 95 subjects (47%) showed evidence of involvement of one or more segments, while the remainder had more extensive pulmonary

involvement. Subjects at Ivanovo had evidence of more severe TB on CXR. As illustrated in Table 1, 135 (68%) subjects had a positive TB culture varying from abundant to minimal growth. Sixty-five (33.5%) subjects had no growth on culture.

Table 1 also reports RAB scores for drug use and sexual risk behavior. The HIV risk scores on the RAB were low, suggesting limited exposure to intravenous (IV) drugs and high-risk sexual behavior in these samples. There was one positive urine toxicology after screening 99 subjects at the St Petersburg site, and only two patients at both sites admitted to recent IV heroin use. This corresponds to finding only one positive HIV test in the Ivanovo sample. These findings are surprisingly low, but may reflect a population that has been chronically ill, with limited exposure and opportunity to engage in high-risk sexual behavior.

Table 2 summarizes the prevalence of alcohol and drug use disorders at the two sites. The majority of the subjects ( $n = 125$ , 62%) met the criteria for current alcohol abuse or dependence. Over half of the subjects reported harmful consequences, loss of control, alcohol craving, physical dependence, increased time spent on drinking, and reduction in other activities. Forty-seven subjects (24%) had had  $\geq 90$  drinks in the previous month, or an average of three or more drinks per day. Over half ( $n = 107$ ) (56%) reported heavy drinking episodes in the previous 30 days. A large proportion of subjects ( $n = 93$ , 44%), however, reported no heavy drinking days. Very few subjects (<5%) met criteria for drug abuse or dependence. The ASI showed high scores for medical problems and employment difficulties.

Patients at each site were treated with four or five anti-tuberculosis drugs. At the St Petersburg site, the 100 patients in the group were treated with INH (99%) RMP (89%), PZA (82%), EMB (75%), SM (60%), prothionamide (39%) and kanamycin (KM, 16%). TB drugs utilized in the Ivanovo group included INH (98%), RMP (97%), EMB (100%), PZA (97%) and KM (4%). A large proportion of subjects also received antioxidants, non-steroidal agents immunomodulators and glucocorticoids.

Table 3 compares patients with chronic/relapsed TB with those newly diagnosed with TB. Patients admitted with chronic TB were considerably older, were more often unemployed, and had higher rates of alcohol problems than the new cases. The adjusted OR for alcohol abuse/dependence (2.56) suggests a moderate relationship between alcohol use disorders and chronic TB.

Table 4 compares patients with and without resistance to one or more anti-tuberculosis drugs. Of 135 subjects, 35 (37.5%) with positive cultures were resistant to one or more drugs; the 65 who did not have a positive culture were not included in the analysis (Table 4). Fifteen cases of drug resistance were reported from Ivanovo and 20 from St Petersburg. Twelve of the 135 positive cultures were not successfully tested for drug resistance due to technical difficulties. Patients with resistant TB bacilli were male, younger and more likely to be unemployed. The OR for the relationship of drug resistance to alcohol dependence was 8.58 (95% CI 2.09-35.32). This finding suggests substantial risk for drug resistance in patients with alcohol problems.

## DISCUSSION

This study provides new information on the prevalence of alcohol use disorders in patients being treated for active TB and the relationship between alcohol use and drug resistance. The study confirmed high rates of alcohol abuse, alcohol dependence and heavy drinking in Russian TB patients. A relationship was observed between alcohol use disorders and resistance to anti-tuberculosis drugs. This report is one of the first studies to document this relationship in patients being treated for active TB.



Low rates of HIV infection and HIV risk behaviors were also observed in the sample (<1%). This is in contrast to other reports that suggest much higher rates of HIV infection in Russian TB patients.<sup>14,15</sup> HIV infection in Russia is primarily related to IV drug use. In comparison to the US and other countries, there has been more limited transmission by sexual contact. As the sample reported in this study had very low rates of drug use, it is not surprising to find low rates of HIV infection. It is unknown whether HIV infection rates will increase in civilian Russian TB hospitals with low rates of drug addiction as HIV becomes more common in the general population.

This study has a number of strengths, including the large sample of patients with TB, the state-of-the-art measures of alcohol and drug use disorders and HIV risk, the administration of measures by skilled, well-trained research staff, and the high rate of participation. The primary limitation is related to the small number of study sites. It therefore needs to be replicated in a larger number of sites throughout different regions (oblasts) in Russia.

The study brings to the forefront a number of clinical and policy issues. First, TB hospitals need to develop specific programs to screen for and detect alcohol use disorders in patients being treated for TB. Second, Russia needs to develop a comprehensive approach to the treatment of alcohol problems in TB patients throughout the country including brief interventions delivered by TB specialists and 6-12-week-day treatment programs utilizing state-of-the-art counseling methods.<sup>16</sup> Third, TB specialists may wish to consider using pharmacotherapy for alcohol dependence, including medications such as naltrexone and acamprosate, which can reduce craving and alcohol use. Fourth, HIV infection and risk has not reached the current population of patients with TB at these two sites. Prevention programs need to be instituted to prevent the spread of HIV infection to this population.

## CONCLUSION

Non-adherence to anti-tuberculosis treatment and drug resistance remain of major public health concern in Russian TB programs. The data presented in this report support the inclusion of comprehensive alcohol programs as a key component of future Russian TB efforts. Intervention trials are needed to test the ability of alcohol treatment programs to improve TB treatment outcomes.

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**Table 1**

## Description of the sample

	Site 1 St Petersburg (n=100) %	Site 2 Ivanovo (n=100) %	Total (N = 200) n(%)
Mean age, years	42.5	38.9	41.5
Age range, years	19-79	19-60	19-79
Male:sex	59	84	143 (72)
Employed	36	31	67 (33)
Duration of TB			
Newcase	67	90	157 (78)
Relapse	19	8	27 (13)
Chronic	14	2	16 (8)
Radiological findings			
Pulmonary infiltration	61	65	136 (63)
Fibrosis and cavities	9	5	14 (7)
Caseous pneumonia	3	1	4 (2)
Pleural effusion only	1	1	2 (1)
Other findings	26	26	52 (26)
TB cultures			
No growth	43	22	65 (33)
Minimal growth	21	23	44 (22)
Moderate growth	28	46	74 (38)
Abundant growth	8	9	17 (8)
Total	100	100	200 (100)
HIV risk			
RAB scores, mean (SD) *			
Sexual risk	3.3 (2.0)	3.5 (2.0)	3.4 (2.0)
Drug risk	0	0.1 (0.6)	0
Total score	3.3 (2.0)	3.6 (2.2)	3.4 (2.1)
Positive HIV serology	0	1	1 (1)
IV heroin use	1	1	2 (1)
Depression score †			
0-10	50	30	80 (40)
11-20	37	48	85 (43)
≥21	13	22	35 (17)

TB = tuberculosis; RAB = risk assessment battery; HIV = human immunodeficiency virus; IV = intravenous.

\* Total RAB scores <5 are considered low risk for HIV exposure.

† Scores 11-20 mild depression, ≥21 moderate depression.



**Table 2**

## Alcohol and drug use disorders

	Site 1 St Petersburg (n=100) %	Site 2 Ivanovo (n = 100)%	Total(N= 200)n (%)
DSM-IV alcohol use disorders			
Alcohol abuse	31	9	40 (20)
Alcohol dependence	24	61	85 (42)
Poly drug abuse/dependence	5	0	5 (3)
No alcohol diagnosis	40	30	70 (35)
Symptoms of alcohol abuse and dependence			
Harmful consequences	59	68	127 (63)
Increased tolerance	58	69	127 (63)
Loss of control	67	26	83 (41)
Alcohol craving	66	26	92 (46)
Alcohol with drawal	57	26	82 (41)
Increased time spent drinking	57	59	106 (53)
Reduction in other activities	57	53	110 (55)
Alcohol use in previous 90 days(drinks/month)			
<10	47	22	69 (30)
10-30	24	16	40 (20)
31-60	10	12	22 (11)
61-90	12	10	22 (11)
≥90	7	40	47 (24)
Number of heavy drinking days in last month (≥ 5 drinks for men and ≥4 drinks for women)			
None	63	30	94 (47)
1-4	31	31	63 (31)
5-10	3	13	25 (12)
≥11	3	9	18 (24)
Addiction severity index (ASI), mean (SD)			
Medical problems	0.48 (0.33)	0.58 (0.28)	
Employment	0.71 (0.27)	0.80 (0.23)	
Alcohol	0.07 (0.15)	0.13 (0.21)	
Drugs	0	0	
Legal problems	0.01 (0.09)	0.02 (0.07)	
Family/social problems	0.12 (0.17)	0.12 (0.15)	
Psychiatric symptoms	0.27 (0.17)	0.12 (0.15)	

DSM-IV diagnostic D- and Statistical Manual for Mental Disorders; <sup>11</sup> SD -standarddeviation.

**Table 3**

Comparison of chronic/relapsed TB cases and new TB cases by age, sex, employment and alcohol use disorders

	Chronic/relapsed ( <i>n</i> = 43)	New cases ( <i>n</i> = 157)	Difference between groups <i>P</i> value	OR (95%CI)(adjusted for age and sex)
Age, years, mean (SD)	49.3 (15.2)	38.4(12.2)	<0.001	
Male sex, <i>n</i> (%)	29(67.4)	114(72.6)	0.51	
Employed, <i>n</i> (%)	5(11.6)	62(39.5)	<0.001	
Number of drinking days, mean (SD)	5.9 (6.7)	4.6(5.5)	0.23	1.07 (1.01-1.14)
Number of heavy drinking days, mean (SD)	3.0(5.2)	3.5(5.3)	0.56	1.06(1.03-1.09)
Alcohol abuse/dependence, <i>n</i>	69.8	63.1	0.42	2.56(1.00-6.54)

TB tuberculosis; OR odds ratio; CI =confidence interval; SD - standard deviation.

**Table 4**  
Comparison of patients with and without TB drug resistance

	Drug resistance (n=35)	No resistance (n = 100)	Difference between groups Pvalue	OR(95%CI)(adjusted for age and sex)
Age, years, mean (SD)	38.4(10.5)	41.2(14.2)	0.64	
Malesex, n (%)	28(80.0)	69(69.0)	0.28	
Employed, n (%)	6(17.1)	34(34.0)	0.08	
Number of drinking days, mean (SD)	6.7(6.0)	5.1(5.7)	0.16	1.04(0.97-1.11)
Number of heavy drinking days, mean(SD)	5.3 (6.3)	3.0 (5.2)	0.04	1.06 (0.99-1.13)
Alcohol abuse/dependence, n (%)	32 (91.4)	61 (61.0)	<0.001	8.58 (2.09-35.32)

TB - tuberculosis; OR = odds ratio; CI = confidence interval; SD - standard deviation