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Research Article

Multidrug Resistant Tuberculosis Cure Predictors

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Abstract

Many parts of the world face a new challenge to control tuberculosis epidemic with the emergence of Multi Drug Resistant Tuberculosis (MDR-TB) and Extensive Drug Resistant Tuberculosis (XDR-TB). We analyzed the data from a prospective study of patients with MDR-TB & XDR-TB treated in Medicines Sans Frontieres (MSF) hospitals in Armenia to identify patients and treatment characteristics that predict cure of MDRTB and XDR-TB. Of 350 patients, 197 (56.4 %) had a history of alcohol use, 130 (37.1%) history of being in prison and 64 (18.4%) were injecting drug users. Out of 350 patients, 37 (10.6 %) were cured and 313 (89.4) were not cured. In multivariate analysis, success was positively associated with treatment duration (OR = 1.1, p = 0.003), moderate alcohol use (OR= 3.5, p = 0.01) and negatively associated with injection drug use (OR = 0.66, p = 0.02) and trend towards negative association with excessive alcohol use (OR= 6.26x10-9, p = 0.99). The proportion of patients achieved cure is very low. Results suggest that, longer the treatment duration and moderate alcohol use better the treatment outcome. Patients with injection drug use had a poor treatment outcome. Excessive alcohol use showed trend towards poor treatment outcome.

Keywords: *Multi Drug Resistant Tuberculosis (MDR-TB); Extensive Drug Resistant Tuberculosis (XDR-TB); Tuberculosis (TB); Treatment outcome; Alcohol; IV drug use*

Introduction

The world now faces a new challenge of tuberculosis (TB) epidemic, due to emergence of Multi Drug Resistant Tuberculosis (MDR-TB) and Extensive Drug Resistant Tuberculosis (XDR-TB) [1,2]. MDR-TB is defined as infecting isolates that are resistant in vitro to isoniazid (H) and rifampicin (R), XDR-TB is defined as resistance to any fluoroquinolone, and 1of 3 injectable second-line drugs (capreomycin, kanamycin and amikacin) [1,3]. According to the Global Tuberculosis 2014 report by World Health Organization (WHO) there were an estimated 480,000 (range: 350,000 - 610,000) new cases of MDR-TB worldwide, and approximately 210 000 (range: 130,000 - 290,000) deaths from MDR-TB [1]. In 2013, WHO estimated that 3.5% of all new TB cases and 20.5% of previously treated cases have MDR-TB [1]. By 2013, XDR-TB has been reported in at least 100 countries and 9% of MDR-TB cases have XDR-TB [1]. WHO estimated that, the proportion of MDR-TB diagnosed of new TB cases is 9.4% and previously treated TB cases is 43% in Armenia [1].

The success rate of MDR-TB treatment globally is low; 48% reported in Global tuberculosis 2014 report [1], 54% reported by Ahuja SD., *et al.* [4], 62% reported by Johnston., *et al.* [5] and 64% reported by Orenstein., *et al.* [6]. MDR-TB success is low as there are limited treatment options and several other factors affecting the cure. To cure an MDR-TB patient, it takes 18 - 24 months with second-line drugs (SLDs), which are less efficacious, more toxic, less tolerated and considerably more expensive [1,7,8]. The other factors that affect the MDR-TB cure are co-infection with HIV [9-13], social factors such as alcohol [7,9,12,14,15] and intravenous drug abuse [10]; socioeconomic factors like poverty and unemployment [16,17]; advanced disease, prior treatment, treatment default [18], resistance to fluroquinolones [9,13-15] positive acid-fast bacilli (AFB) smear at the start of treatment, absence of early culture conversion, number of

drugs in the regimen [5,6,19-21] and programmatic factors such as poor provider communication and barriers to accessing care [22]. We analyzed the data from a prospective study of patients with MDR-TB & XDR-TB treated in Medicines Sans Frontiers (MSF) hospitals in Armenia who received an individualized treatment regimen (ITR) based on drug sensitivity testing (DST) results to identify patients and treatment characteristics that predict cure of MDR-TB and XDR-TB and to determine if there are specific identifiable groups who are at increased risk of failure to cure.

Methods

Study settings

This was an original study of Medicines Sans Frontieres organization. This is an observational prospective cohort study of 350 patients with MDR-TB & XDR-TB treated in MSF hospitals in Armenia. Tuberculosis database program: Epi Info (Version-6) was used to have universal data registry and ensure to have correct and updated information in all MDR-TB program centers. Data was collected in Armenia Hospitals from 2001 to 2008. This study was conducted by MSF and WHO Green light committee approved it. Informed consent was taken from patients before they were included in the study. Analysis of this study data was also approved by Public Health Department at Icahn School of medicine at Mount Sinai, New York.

Patient selection process

The aim of a MDR-TB treatment program was to make treatment accessible to as many patients who needed treatment. However there were some criteria's and preliminary steps before they were included into the program. Decision to include or exclude a patient, was a team decision and is discussed by the physician with the other care givers such as nurse, health educator, social worker and the psychiatrist.

Inclusion and exclusion criteria

Included only those patients who meet the geographic criteria of living in the region, after undergoing through a preliminary introduction and agreed for the treatment. In preliminary introduction patients were informed about the disease process, length of the treatment, directly observed treatment, need for hospitalization, side effects, expected outcomes and the need of follow-up. Any questions or difficulties experienced by the patient were addressed. Patients are required to commit to adhere to the treatment and complete the course of treatment. Patients who have severe co-existing illnesses and who seemed to not tolerate the second line Anti-TB medications, in terminal clinical conditions were excluded. The patient's family is also implicated in supporting the patient and should be involved in the preliminary information sessions. Factors that could result in poor or difficult adherence for the patient, such as addictions (drug, alcohol) and with previous history of poor treatment adherence, coping mechanisms and support systems were discussed before inclusion. Female patients should agree together with their partner to use a reliable method of contraception to avoid pregnancy during the full course of treatment. Second line drugs reduce the serum concentration of oral contraceptives therefore injectable contraception is preferred method. Pre-existing and severe co-existing illness such as renal and hepatic insufficiency, uncontrolled seizure disorder, or known allergies to second-line drugs, which could prevent the managing physician from prescribing an effective second-line treatment regimen were excluded. Program ensured prison patients to have continuity of treatment.

General treatment principles

All patients received an individualized treatment regimen (ITR) based on DST results. An Empiric Treatment Regimen (ETR) is used on a temporary basis for certain suspect cases until full DST results become available. Treatment is given under direct observation (DOT). Treatment is initiated with small doses of each drug and increased to the planned dose over 3 to 10 days. Maximum doses of second-line drugs are used whenever possible, with immediate and aggressive treatment of side effects. Therapy is given 6-7 days per week and up to twice daily; no intermittent therapy with second-line drugs is given during either intensive or continuation phase except for parenteral agents, which may be given 3 times weekly when side effects such as renal insufficiency arise. When treatment fails or a relapse occurs, the original regimen is continued with addition of 2 new drugs until new susceptibility data are obtained. The minimum treatment duration of MDR-TB treatment is 21-24 months or 18 months after the patient becomes permanently smear and culture negative, whichever is longer.

Criteria for treatment interruption included 1. Impossible to continue proper treatment due to intolerance to second-line drugs 2. The physician may also determine after 6 to 12 months in case of unfavorable evolution, using all clinical and microbiologic evidence available, that further therapy is futile and only supportive care should be offered. 3. The feasibility and the benefit of the surgical option have to be considered before proposing the permanent interruption of treatment. 4. Poor adherence to treatment (frequent treatment interruptions, addictions) Aggressive, disruptive or criminal behavior during treatment could be considered as dismissal criteria.

Case definitions for end of treatment outcomes

Cured: An MDR-TB patient who has completed treatment and has been consistently culture-negative (with at least five results) for the final twelve months of treatment. If only one positive culture is reported during that time and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures, taken at least 30 days apart.

Completed: An MDR-TB patient who has completed treatment but does not meet the definition for cure due to lack of bacteriological results (i.e., fewer than five cultures were performed in the final twelve months of therapy).

Death: An MDR-TB patient who dies for any reason during the course of MDR-TB treatment.

Treatment failure: Treatment will be considered to have failed if two or more of the five cultures recorded in the final twelve months are positive, or if any one of the final three cultures is positive. Treatment will also be considered to have failed if a clinical decision has been made to terminate treatment early due to poor response or adverse events.

Treatment default: An MDR-TB patient whose MDR-TB treatment was interrupted for two or more consecutive and also includes the patients removed from treatment by physicians.

Transfer out: An MDR-TB patient who has been transferred to another reporting and recording unit and for whom the treatment outcome is unknown.

Still on treatment: Patient still in treatment at the time of the cohort analysis.

Statistics

To look for correlations between the patients and treatment characteristics that predict cure of MDR-TB and XDR-TB, we used univariate student t-test and chi-square tests. An independent-samples t-test was conducted to compare between the success and failure groups with age, treatment duration, days to smear conversion, days to culture conversion, days to end hospitalization, days to end injection phase, Previous DOTS treatment, Previous DOTS Plus treatment, number of people living in the same house, and number of children living in the same house. A chi-square test was conducted to compare between the success and failure groups with risk factors (nominal variables) such as previous TB treatment, drug sensitivity testing, marital status, employment status, ever been in prison, injection drug user, prostitution, homeless, healthcare worker, migrant worker, traveler (out of Armenia), previous contact with MDR-TB case, tobacco use and alcohol use.

Treatment outcome variables were categorized into a dichotomous variable as success and failure. Success included all cured cases and all other treatment outcomes such as treatment completed, failed, default (whose treatment was interrupted for 2 consecutive months or more), transfer out and unknown status were included in failure group. Bivariate analysis using Independent t-test for continuous variables and chi-square for discrete variables was performed taking success and failure as dependent variables and other variables as independent or covariate variables. To check out the hypothesis, we did logistic regression. All values are expressed as mean ± SD or valid percentages (%). All statistical analyses were achieved using the Statistical Package for Social Sciences (SPSS) 21.0 software (SPSS Inc., Chicago, Illinois). Missing data were not replaced or imputed. A P value < .05 was considered significant.

Results

Observation data for 350 patients from 2001 to 2008 were analyzed. There were 282, (80.6%) males and 68 (19.4%) females; mean age was 38 ± 13 years. Most patients were unemployed 255 (73.1%), lived in their own homes 338 (97.7%), lived with 3 or more people

(range 1-9) and had one child in their house (range 0-5). Sixty-four (18.4%) have history of intravenous drug use (IDU) and 130 (37.1%) have history of being in prison, 197 (56.0%) had a history of alcohol use -162 (46%) moderate, 35(10%) excessive, and 218 (62.3%) had a history of tobacco use. Of all 350 patients, 78 (22.6%) reported previous contact with MDR-TB patients (Table 1).

Variables	Value ± SD or Percentage
Age (years)	38 ± 13
Male (%)	80.6
Female (%)	19.4
Migrant worker (%)	3.5
Health care worker (%)	0.9
Homeless (%)	2.3
Marital status (%)	
Married	50.7
Living together	0.9
Single	36
Divorced	6.9
Widowed	4
Separated	1.4
Employment status (%)	
Employed	16.3
Pensioner	3.2
Student	2.3
Unemployed	73.1
Household	4
Other	1.1
Tobacco use (%)	62.6
Alcohol use (%)	56.4
Alcohol Severity (%)	
None	43.6
Moderate	46.4
Excessive	10
Injection drug user (%)	18.4
Prostitution (%)	0.3
Ever been in prison (%)	37.2
Traveller (out of Armenia) (%)	10.7
Contact with MDR-TB case (%)	22.6
Number of people living in the same house	3 ± 1.8
Number of children less than 15 living in the same house	1 ± 1.02

SD: Standard deviation

Table 1: *Patient characteristics.*

The mean treatment duration was 12.75 ± 9.1 (1 - 44.9) months. The average number of days to initial smear conversion was 114.1 ± 118.4 days, number of days to initial culture conversion was 112.2 ± 115.03, number of days to end of hospitalization phase was 140.31 ± 133.36 and number of days to end of injection phase was 240.04 ± 118.7. 344 (98.3%) patients reported to previous TB treatment, the average number of times the patient has received DOTS treatment is 2.07 ± 1.6, the average number of times the patient has received DOTS PLUS treatment is 0.12 ± 0.4 and 90.8% have not received DOTS PLUS treatment previously. On Drug Sensitivity Testing, before the start of treatment 284 (93.4%) were resistant to Isoniazid (H), 239 (79.7%) were resistant to Rifampin (R), 243 (80.7%) were resistant to Ethambutol, 73 (47.7%) were resistant to Pyrazinamide (P) and 265 (89.2%) were resistant to Streptomycin (S) (Table 2).

Variables	Value ± SD or Percentage
Treatment duration (months)	12.75 ± 9.1
Days to smear conversion	114.1 ± 118.4
Days to culture conversion	112.2 ± 115.03
Days to end hospitalization	140.3 ± 133.4
Days to end injection phase	240.04 ± 118.7
Previous TB treatment (%)	98.3
No. of previous DOTS treatment	2.07 ± 1.6
No. of previous DOTS treatment (%)	
0	2
1	43.1
2	28.4
3	13.8
4	7.5
5	2.6
6	1.1
7	0.6
No. of previous DOTS Plus treatment	0.12 ± 0.4
No. of previous DOTS Plus treatment (%)	
0	90.8
1	6.9
2	2
3	0.3
Treatment interruption (%)	0.9
Drug Sensitivity Testing (DST) (%)	
Isoniazid (H)	
Resistant	93.4
Sensitive	4.9
Rifampin (R)	
Resistant	79.7
Sensitive	19.7
Ethambutol (E)	

Resistant	80.7
Sensitive	18.9
Pyrazinamide (Z)	
Resistant	47.7
Sensitive	51.6
Streptomycin (S)	
Resistant	89.2
Sensitive	10.8

SD: Standard deviation

Table 2: *Patient management characteristics.*

Assessment of treatment outcomes showed that 37(10.6 %) patients were cured, 36 (10.3 %) completed therapy, 31 (8.9%) died, 13 (3.7 %) treatment failed, 64 (18.3 %) defaulted and 29 (8.3 %) were transferred out (Table 3).

Treatment outcome	Percentage
Cured	10.6
Completed	10.3
Death	8.9
Failure	3.7
Default	18.3
Transfer out	8.3
Unknown	39.7

Table 3: *Treatment outcomes.*

In bivariate analysis followed by logistic regression, success was positively associated with treatment duration (OR = 1.1, 95% CI (1.03 - 1.18), p = 0.003), moderate alcohol use (OR= 3.5, 95% CI (1.34 - 9.15), p = 0.01 and negatively associated with injection drug use (OR = 0.66, 95% CI (0.006 - 0.7), p = 0.02) and trend towards negative association with excessive alcohol use (OR= $6.26x10^{-9}$, 95% CI (0.0 - ∞), p = 0.99 (Table 4 and 5).

	Success			Failure				
	n	Mean	SD	n	Mean	SD	P - Value	95% CI
Age	37	38.16	12.04	313	38.27	13.01	0.96	-4.5 - 4.3
Treatment duration (months)	37	22.35	6.83	313	11.61	8.68	<0.001	7.8 -13.6
Days to smear conversion	32	121.3	89.57	143	107.87	119.6	0.55	-30.8 -57.7
Days to culture conversion	35	104.4	69.20	129	108.95	119.4	0.83	-46.2- 37.2
Days to end hospitalization	33	231.2	168.50	232	121.25	128.5	<0.001	60.9 - 159.1
Days to end injection phase	36	236.3	104.47	145	241.03	121.0	0.83	-48.1- 38.6
Previous DOTS treatment	37	2.00	1.22	311	2.07	1.710	0.80	-0.64 - 0.5
Previous DOTS Plus treatment	36	.03	0.16	311	0.13	0.421	0.15	-0.24 - 0.04
Number of people living in the same house	37	2.73	1.75	311	3.21	1.82	0.13	-1.1 - 0.15
Number of children living in the same house	37	0.76	1.09	312	0.72	1.01	0.85	-0.31- 0.38

	Success	Failure	Total	p–value	
Isoniazid	Resistant	(36) 100.0%	(248) 92.5%	284 93.4%	.41
	Sensitive	(0) 0%	(15) 5.6%	(15) 4.9%	
Rifampin	Resistant	(25) 69.4%	(214) 81.1%	(239) 79.7%	.19
	Sensitive	(11) 30.6%	(48) 18.2%	(59) 19.7%	
Ethambutol	Resistant	(30) 83.3%	(213) 80.4%	(243) 80.7%	.87
	Sensitive	(6) 16.7%	(51) 19.2%	(57) 18.9%	
Pyrazinamide	Resistant	(3) 50.0%	(70) 47.6%	(73) 47.7%	.97
	Sensitive	(3) 50.0%	(76) 51.7%	(79) 51.6%	
Streptomycin	Resistant	(34) 94.4%	(231) 88.5%	(265) 89.2%	.28
	Sensitive	(2) 5.6%	(30) 11.5%	(32) 10.8%	
Previous TB treatment	Yes	(37) 100.0%	(307) 98.1%	(344) 98.3%	.39
	No	(0) 0%	(6) 1.9%	(6) 1.7%	
Marital status	Married	(21) 56.8%	(155) 50.0%	(176) 50.7%	.50
	Living Together	(0) 0%	(3) 1.0%	(3) 0.9%	
	Single	(14) 37.8%	(111) 35.8%	(125) 36.0%q	
	Divorced	(0) 0%	(24) 7.7%	(24) 6.9%	
	Widowed	(2) 5.4%	(12) 3.9%	(14) 4.0%	
	Separated	(0) 0%	(5) 1.6%	(5) 1.4%	
Employment status	Employed	(7) 18.9%	(50) 16.0%	(57) 16.3%	.63
	Pensioner	(1) 2.7%	(10) 3.2%	(11) 3.2%	
	Student	(0) 0%	(8) 2.6%	(8) 2.3%	
	Unemployed	(29) 78.4%	(226) 72.4%	(255) 73.1%	
	Housework	(0) 0%	(14) 4.5%	(14) 4.0%	
Ever been in prison	Yes	(17) 45.9%	(113) 36.2%	(130) 37.2%	.24
	No	(20) 54.1%	(199) 63.8%	(219) 62.8%	
Injection drug user	Yes	(2) 5.7%	(62) 19.9%	(64)18.4%	.04
	No	(33) 94.3%	(250) 80.1%	(283) 81.6%	
Prostitution	Yes	(0) 0%	(1) 0.3%	(1) 0.3%	.74
	No	(34) 100.0%	(304) 99.7%	(338) 99.7%	
Homeless	Yes	(1) 2.8%	(7) 2.3%	(8) 2.3%	.84
	No	(35) 97.2%	(303) 97.7%	(338) 97.7%	
Health Worker	Yes	(0) 0%	(3) 1.0%	(3) 0.9%	.55
	No	(36) 100.0%	(307) 99.0%	(343) 99.1%	
Migrant worker	Yes	(1) 2.8%	(11) 3.5%	(12) 3.5%	.81
	No	(35) 97.2%	(299) 96.5%	(334) 96.5%	
Traveler (out of Armenia)	Yes	(2) 5.6%	(35) 11.3%	(37) 10.7%	.29
	No	(34) 94.4%	(275) 88.7%	(309) 89.3%	
Contact with MDR-TB case	Yes	(3) 8.3%	(75) 24.3%	(78) 22.6%	.03
	No	(33) 91.7%	(234) 75.7%	(267) 77.4%	

Tobacco use	Yes	(27) 73.0%	(191) 61.4%	(218) 62.6%	.16
	No	(10) 27.0%	(120) 38.6%	(130) 37.4%	
Alcohol use	Yes	(27) 73.0%	(170) 54.5%	(197) 56.4%	.03
	No	(10) 27.0%	(142) 45.5%	(152) 43.6%	

n: Sample size, SD: Standard deviation, CI: Confidence interval

Table 4: *Association between treatment successes to failure.*

Variables	OR (95% CI)	P - value
Treatment duration	1.1 (1.03 - 1.18)	0.003
Days to end hospitalization phase	1.0 (0.99 - 1.01)	0.26
Previous Contact with MDR-TB	0.32 (0.07 - 1.49)	0.15
Alcohol Severity		
Moderate	3.5 (1.34 - 9.15)	0.01
Excessive	$6.26x10^{-9}$ (0.0 - ∞)	0.99
Injection drug users	0.66(0.006 - 0.7)	0.02

OR: Odds Ratio, CI: Confidence interval

Table 5: *Final multivariate model.*

Discussion

MDR TB treatment is a challenge as there are limited treatment options. MDR-TB treatment is left with fewer treatment options due to the emergence of resistant strains. To cure an MDR-TB patient, it takes 18 - 24 months with second-line drugs (SLDs) as reported in Global tuberculosis 2014 report [1]. Second line drugs are less efficacious, more toxic, less tolerated and considerably more expensive [1,7,8] which could result in more serious adverse effects, treatment defaults, extending the treatment duration. Our study showed longer the treatment duration better the treatment outcome, which was consistent with study done by Ahuja., *et al*. [4] and global tuberculosis 2014 report [1]. Our patient received empiric treatment initially and then tailored based on drug sensitivity testing and adverse effects to achieve success resulting in lengthy treatment.

Literature showed alcohol and illicit drug use to be the important risk factors for contracting the disease and poor treatment outcome and also they have been implicated as the cause of TB epidemics in many countries. Few studies suggested that low to moderate alcohol intake is not associated with increased risk of TB disease [15]. However, there seem to be a substantial risk increase among people who drink more than 40g alcohol per day, and or have an alcohol use disorder. This was clearly demonstrated by many studies and systematic reviews [7,14,15,23]. The role of heavy alcohol consumption and illicit drug use as a risk factor for contracting tuberculosis can be explained by specific social mixing patterns in settings such as bars, shelters for homeless, prisons, and social institutions as well as by direct toxicity to the immune system [5]. The effects of alcohol and drug use on the immune system include impairment of cell mediated immunity and macrophage function that reduce the ability to clear the infection and result in less favorable outcome [5,24,25]. Our data showed correlation between moderate alcohol use with treatment success and excessive alcohol use showed trend towards treatment failure. This trend was probably secondary to very low number of patients with excess alcohol use (35, 10%) compared to moderate alcohol use 162 (46.4). Many studies have demonstrated the beneficial effects of moderate alcohol use in lowering myocardial infarction, heart failure and ischemic stroke rates and reduced risk of dementia, diabetes and osteoporosis [26-28], however there were no studies looking at treatment success of TB or MDR-TB with moderate alcohol use. Our data showed correlation between injection drug use with treatment failure and is consistent with studies done by Bendayan., *et al*. [7] and Deiss., *et al*. [29].

Key to prevent the spread and achieve the cure of MDR-TB and XDR-TB is implementation of proven strategies to control alcoholism and intravenous drug use. Some of the proven strategies are: 1. a. Limiting alcohol consumption by increasing the taxes [30,31,] b. Im-

posing limits on days of sale for off-premises settings (e.g., grocery, convenience or liquor stores) [32,33] c. Regulation of Alcohol Outlet Density [34]. 2. Screening individuals for excessive drinking, drug use and delivering a brief intervention, which provides personalized feedback about the risks and consequences of excessive drinking and drug use [35]. 3. Raising awareness through community activities and participation [35]. 4. Political commitment in implementing strict policies in controlling alcohol and drug use at national and municipal level [35].

Limitations

This study has several limitations like small sample size, limited to a region, only the patients with MDR-TB & XDR-TB who could tolerate the treatment and willing to complete the treatment were included in the study. Individualized treatment was given based on patient profile instead of randomization of treatment, there were no consistent follow-ups and some have left without treatment completion. HIV disease is an important risk factor for acquiring the disease and achieving cure of either susceptible or resistant tuberculosis or their status on HIV is unknown. Finally there was large amount of patients with unknown treatment status who were included in failure group resulting lower percentage of cure.

This study highlights the need for randomized studies with large sample size evaluating the individualized treatment regimens, moderate alcohol consumption and TB or MDR-TB treatment outcomes and urgent need for more efficacious, well tolerated, drug regimens to cure MDR-TB.

Conclusion

Analysis of data showed that, longer the treatment duration and moderate alcohol use (a daily intake of any kind of alcohol beverage less than 3 glasses or 40 grams), better the treatment outcome and higher the injection drug use, lower the success. Excessive alcohol use (a daily intake of any kind of alcohol beverage more than 3 glasses), showed trend towards negative correlation with success, suggesting excessive alcohol use had poor treatment outcome.

The key for success in prevention and cure of MDR-TB and XDR-TB is implementation of public health strategies to control alcoholism and intravenous drug use.

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