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Time to sputum conversion in multidrug-resistant tuberculosis patients in Armenia: retrospective cohort study

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ABSTRACT

OBJECTIVE: To characterize time to sputum conversion among patients with multidrug resistant tuberculosis who were enrolled into second-line tuberculosis treatment program; to identify risk factors for delayed sputum conversion. DESIGN: Retrospective cohort study designed to identify the factors associated with sputum conversion. Survival analysis was performed using Kaplan-Meier estimator to compute estimates for median time to sputum conversion and Cox proportional hazards model to compute hazard ratios (HR). RESULTS: Sputum conversion from positive to negative was observed in 134 out of 195 cases (69%). Among these who converted the median time to conversion was 3.7 months. Factors independently associated with time to sputum conversion in the proportional hazards model were: male sex (HR=0.51, 95% CI 0.32-0.81), ofloxacin-resistant tuberculosis (HR = 0.45, 95% CI 0.26-0.78) and first period of recruitment into second-line treatment (HR= 0.69, 95% CI 0.47-1.01). CONCLUSION: Time to sputum conversion in patients with multidrug-resistant tuberculosis in Armenia was 5.8 months (range 0.5-17.0 months). High level of ofloxacin resistance was the main reason for compromised response to treatment. Patients with a poor resistance profile and males should be targeted with more aggressive initial therapy.

Key words: DOTS-Plus, MDR-TB, sputum conversion, Armenia

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Introduction

Armenia is among the 10 countries with the highest prevalence rate of multidrug-resistant tuberculosis (MDR-TB) reaching up to 9.4% among never treated patients and 43.2% among previously treated cases (WHO 2010). This is an enormous public health challenge for Armenia, since the treatment of MDR TB is very costly, takes longer, and has much poorer outcomes compared to treatment for sensitive TB (Johnston et al., 2009; Sharma a et al., 2006; Fox et al., 2011).

Starting from September 2005 Médecins Sans Frontières supported DOTS-Plus pilot project in collaboration with the National Tuberculosis Program (NTP) to treat patients with drug-resistant tuberculosis. By December 2009, 290 patients had been enrolled in the drug-resistant treatment program.

Sputum conversion is one of the most important interim indicators of pulmonary TB treatment efficacy (Laerson et al., 2005, WHO 2008). Early conversion is very important to prevent transmission of MDR TB, reduce hospitalization time, and reduce cost related to infection control measures. There is some evidence also that delayed sputum conversion is associated with amplifications of drug resistance (Temple et al. 2008).

Few published studies had ever examined sputum conversion among MDR TB patients which demonstrated quite different patterns and risk factors of conversion (Holtz et al., 2006, Qazi et al., 2011).

The aims of our study were to determine the overall time to sputum conversion pattern among 195 MDR TB patients enrolled into Armenia DOTS-Plus program and to identify the predictors of sputum conversion.

Study Population And Methods

Study population

The study population consisted of patients with MDR TB enrolled into the second-line treatment program. All patients enrolled into second-line TB treatment program in Armenia between September 2005 and end of 2009 were screened for eligibility for the study. Seventy-one patients were excluded as they had other types of drug-resistant tuberculosis than MDR TB. Nineteen patients with MDR TB were excluded, because they missed sputum culture being taken on a monthly basis before their conversion and exact time of conversion was not known. Five patients had negative sputum culture at enrollment into second line therapy. This gave a final study population of 195 patients. Patients were censored at death, default, failure, or on the arrival of 30 June 2010, whichever came first.

Definitions

We applied WHO standard definitions for TB classification, treatment and outcome. TB with isolates resistant to at least two main drugs, rifampicin and izoniasid were classified as MDR. Isolates resistant to any fluoroquinolone and at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin), in addition to multidrug-resistance were classified as extensively resistant TB (XDR TB). Sputum conversion was defined first of two sets of consecutive negative smears and cultures, from samples collected at least 30 days apart. The date of the first set of negative cultures and smears was used as the date of conversion**.** An MDR TB patient whose MDR-TB treatment was interrupted for 2 or more consecutive months for any reason was classified as defaulter (WHO 2008). Survival time was defined as the time from the date of start of second-line treatment to initial sputum conversion or the date of the sample for last smear and culture taken before the death or default or treatment failure or end of study (30 June, 2010).

Treatment regimen and monitoring of treatment

The Armenia MDR treatment program applied a combination of empiric and individualized treatment regimen for confirmed MDR TB patients. The initial regimen consisted of five drugs, including at least one injectable anti-TB drug (kanamycin or capreomycin), at least one later-generation fluoroquinolone (levofloxacin or moxifloxacin), oral bacteriostatics (protionamid, cycloserin or PAS), pyrazinamid and ethambutol. At initiation of treatment a sample was taken for second-line drug-sensitivity test (DST). If there was any indication then the treatment regimen was modified to ensure that at least five drugs with confirmed susceptibility are administered during the intensive phase of treatment. Duration of treatment was guided by culture conversion. The intensive phase continued for a minimum of six months, and for at least four months after the patient first became and remained smear- and culture- negative. Overall duration of treatment was at least 18 months following culture conversion. Regimen during continuation phase consisted from at least four drugs, out of which three with proven susceptibility and pyrazinamid (Ministry of Health of Republic of Armenia 2010). Over 90% of patients were hospitalized during the intensive phase of treatment. Administration of pharmaceuticals was directly observed during this period. In addition these patients received nutritional and psychosocial support. Sputum smear, culture and DST during the intensive phase of treatment were conducted monthly. Treatment was adapted based on most recent DST result and clinical progress.

The outcome of interest of the study was time to sputum conversion. Risk factors included: age, sex, history of TB treatment, incarceration status, bacillary load and negative sputum smear at the beginning of treatment, drug-resistance pattern at initiation of treatment and period of enrollment into MRD TB treatment. For this study the dataset maintained at the National TB reference laboratory (NRL) was used which was linked with the Borstel Supranational laboratory (SRL) results datasheets.

Laboratory methods and measurements

Sputum specimens underwent initial processing and culturing at National reference laboratory (NRL) of Armenia. For each sample two culture

tubes were used: one with solid Lowenstein-Jensen (LJ) media and one with liquid media (Middlebrook). For liquid media MGIT 960 (BD Diagnostics, Sparks, MD, USA) was used according to standard protocols (Strong et al., 1981; WHO 2006). DST for first-line drugs was performed on liquid media using the MGIT 960 system. For second-line drugs the classic proportional method on LJ media was used. In this study up to the end of August 2008 DST was conducted at Borstel SRL. Testing results starting from September 2008 were derived from the Armenia NRL. External proficiency testing of DST for the Armenia NRL was conducted on an annual basis by Borstel SRL. Since 2005 the agreement of isoniazid and rifampicin DST was evaluated 100%.

Statistical analysis

STATA software version 11 (Stata Corp, College Station, TX, USA) was used for statistical analysis. Twelve variables had missing values. Univariate analyses were conducted using all available data. To assess whether data were missing randomly, subjects with missing data were compared with subjects without missing data on important independent and dependent variables. To allow for adjustment by time trends patients were classified into two groups by mean of study observation period (30 January 2008).

Survival analysis was performed to compare the time to sputum conversion by various levels of variables. For each categorical variable Kaplan-Meier survival curves were constructed stratified for each level of the variables. The log-rank test was used to test for statistical differences in the observed time to sputum conversion. Unadjusted and adjusted hazard ratios for conversion were calculated from a Cox proportional hazard model after testing for the assumption of constant proportional hazards. For continuous variables (age and number of drugs resistant at treatment initiation) likelihood ratio test (LRT) for departure from linearity was tested. Factors associated with time to sputum conversion at 0.1 level in Kaplan-Meier analysis were taken forward to the multivariate Cox regression model. In the final model possible interactions between risk factors were tested.

The current analysis has been approved by London School of Hygiene and Tropical Medicine ethics committee. Permission was received from the National Tuberculosis Program in Armenia on the use of the NRL dataset.

Results

Demographic and bacteriological characteristic :

Out of 195 patients studied 164 (84.1%) were men. The mean age of women was 35.0 years (range 17 to 68) and of men 41.9 (range 16 to 81). Sixteen (8.2%) patients were in prison, and 77 (40%) had received TB treatment before the current episode of MDR TB. Initial isolates were resistant to a median of 5 drugs (ranging from 2 to 10 drugs), 89 (45.6 %) patients at initiation of treatment had resistance to at least one second-line drug and 22 (11.3%) tested as XDR TB patients (Figure 1).

Conversion pattern:

Out of 195 patients 134 (68.7%) achieved sputum conversion. By the end of the second month 10.8% of patients achieved conversion, by the end of the 3rd month 21.54% (42 patients) and by the end of the 6th month 49.7% of patients had initial sputum conversion. The last conversion was observed on the 17th month after the start of second-line treatment.

The median time for sputum conversion among these who converted was 3.7 months (ranging from 0.5 to 17.0 months) and median time of conversion among all patients was 5.8 months (Figures 2A, 2B, 2C and 2D).

In Kaplan-Meier survival analysis high colony count, ofloxacin resistance, ethambutol resistance, extensively drug-resistant tuberculosis, number of drug resistant at initiation of treatment was associated with longer time to conversion (Table 1). Resistance to streptomycin, and kanamycin were also associated with delayed sputum conversion at borderline statistically significant levels. Patients recruited into the first half of study period into MDR treatment program had on average a longer conversion period compared to those that started their treatment during the second half. Age, previous tuberculosis treatment, negative sputum smear at initiation of treatment, resistance to PAS, amikacin and pyrazinamide were not associated with time to sputum conversion.

Table 1. Factors associated with time to sputum culture conversion in MDR TB patients, Armenia 2005-2009 (univariate analysis)							
	No. of Patients	Converted (134)		Not converted (61)		Median duration of conversion* (months)	P value (log-rank test)
Variables		Number	(%)	Number	%		
Entire group	195	134	(68.7)	61	(31.3)	5.8	
Sex							0.014
Female	31	26	(83.9)	5	(16.1)	3.97	
Male	164	108	(65.9)	56	(34.1)	6.3	
Age, y							0.326
<= 40 years	93	66	(71.0)	27	(29.0)	4.20	
>40 years	102	68	(66.7)	34	(33.3)	6.97	
History of previous treatment							0.928
Yes	77	52	(67.5)	25	(32.5)	5.63	
No	116	81	(69.8)	35	(30.2)	5.83	
Missing data	*2*	*1*	(50.0)	*1*	(50.0)		
Negative sputum smear at the initiation of treatment							0.143
Yes	13	12	(92.3)	1	(7.7)	5.97	
No	170	115	(67.6)	55	(32.4)	3.90	
Missing data	*12*	*7*	*(58.3)*	*5*	(41.7)	7.40	
Colony count at initial culture							0.054
1+ or 2+	75	53	(70.7)	22	(29.3)	4.60	
3+ or 4+	76	46	(60.5)	30	(39.5)	9.23	
Missing data	*44*	*35*	*(79.5)*	*9*	(20.5)	4.73	
Number of drugs resistant to at treatment initiation							<0.001
>=7 drugs	43	20	(46.5)	23	(53.5)	-	
5-6 drugs	62	44	(71.0)	18	(29.0)	5.63	
2-4 drugs	90	70	(77.8)	20	(22.2)	4.23	
Resistance to streptomycin							0.0884
Yes	186	125	(67.2)	61	(32.8)	5.83	
No	9	9	(100.0)	0	0.0	4.23	
Resistance to ethambutol							0.0363
Yes	129	82	(63.6)	47	(36.4)	6.13	
No	66	52	(78.8)	14	(21.2)	4.20	
Resistance to kanamycin							0.085
Yes	32	14	(43.8)	18	(56.3)	16.97	
No	37	25	(67.6)	12	(32.4)	9.23	
Missing data	*127*	*95*	*(74.8)*	*32*	(25.2)	*4.2*	
Resistance to ofloxacin							0.015

Yes	31	15	(48.4)	16	(51.6)	15.83	
No	130	94	(72.3)	36	(27.7)	5.33	
Missing data	*34*	*25*	*(73.5)*	*9*	(26.5)	*3.47*	
Resistance to capreomycin							493
Yes	33	19	(57.6)	14	(42.4)	6.53	
No	112	76	(67.9)	36	(32.1)	6.26	
Missing data	*50*	*39*	*(78.0)*	*11*	(22.0)	*3.97*	
Resistance to ethionamide							0.152
Yes	44	25	(56.8)	19	(43.2)	8.07	
No	101	70	(69.3)	31	(30.7)	6.03	
Missing data	*50*	*39*	*(78.0)*	*11*	(22.0)	*3.97*	
Resistance to amikacin							
Yes	41	22	(53.7)	19	(46.3)	6.97	0.158
No	102	73	(71.6)	29	(28.4)	6.13	
Missing data	*52*	*39*	*(75.0)*	*13*	(25.0)	*4.53*	
XDR TB							0.003
Yes	*22*	8	(36.4)	14	(63.6)	-	
No	*139*	126	(72.8)	47	(27.2)	5.63	
Missing data	34	25	(67.6)	12	(32.4)	*3.47*	
Treatment initiation period							0.029
Early period (up to 31 Jan, 2008)	84	55	(65.5)	29	(34.5)	6.97	
Late period (after 1 Feb, 2008)	111	79	(71.2)	32	(28.8)	4.6	
**As determined by Kaplan-Meier estimation*							

Table 2. Adjusted hazard ratios for associations for variables with time to initial sputum conversion in the final Cox model for 161 MDR TB patients

Variables	Crude Hazard ratio* (95% CI)	P value	Adjusted hazard ratio† (95% CI)	P value of Wald test	
Sex	0.54 (0.34-0.85)	0.007	0.51 (0.32-0.81)	0.004	
Age group	0.82 (0.56-1.20)	0.310	0.88 (0.60-1.30)	0.529	
Resistance to ofloxacin	0.35 (0.17-0.72)	0.004	0.45 (0.26-0.78)	0.005	
Treatment initiation period	0.74 (0.50-1.08)	0.115	0.69 (0.47-1.01)	0.057	

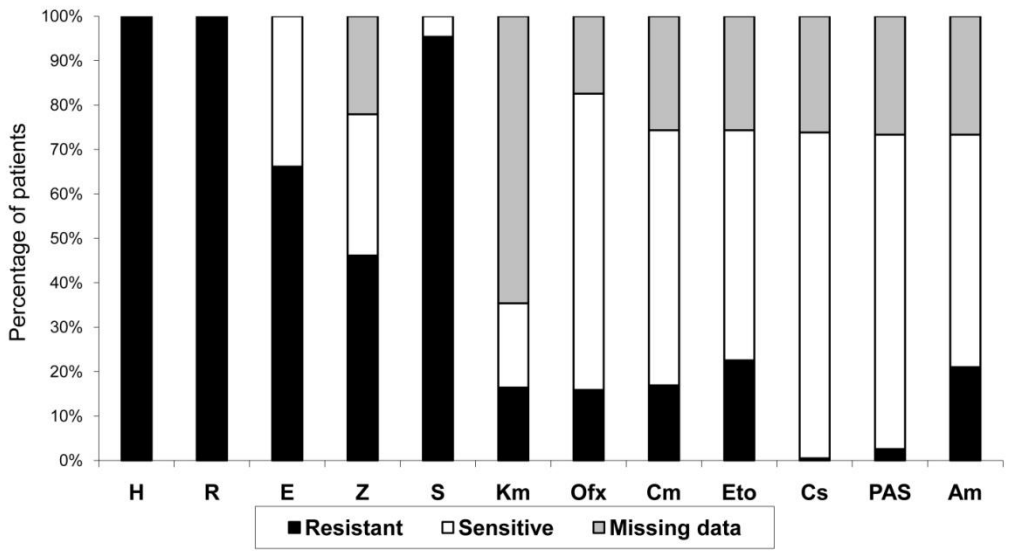
**Excluding observations with missing value for ofloxacin resistance , † Adjusted for all other variable in the final model*

All variables that showed a significance level of p<0.1 in Kaplan-Meier analysis were tested in a multivariate Cox regression model along with age group as a potential confounder. The final Cox regression model included the variables sex, age, infection with strains resistant to ofloxacin and period of recruitment into treatment (Table 2). Due to collinearity with "resistance to ofloxacin" variables "number of drug resistant at the beginning of treatment" and "XDR TB" were not included in the final model. "Colony count at initial culture", "resistance to ethambutol", and "resistance to streptomycin" did not improve the model fit.

According to the final Cox model adjusting for confounding for other variables, males had a rate of conversion 51% of that of females. Patients infected with strains resistant to ofloxacin had a rate of conversion 45% of that of those without

ofloxacin resistance. Patients that started their treatment in the first period of recruitment had a rate of 69% of that recruited at the late stage of program (Table 2).

Figure 1. Drug resistance at initiation of second-line treatment among 195 multidrug-resistant tuberculosis patients



H= isoniazid, **R**=rifampicin, **E**=ethambutol, **Z**=pyrazinamide, **S**=streptomycin, **Km**=kanamycin, **Ofx**=ofloxacin, **Cm**=capreomycin, **Eto**=ethionamide, **Cs**=cycloserine, **Am**=amikacin.

Figure 2A. Sputum conversion in MDR TB patients (n=195)

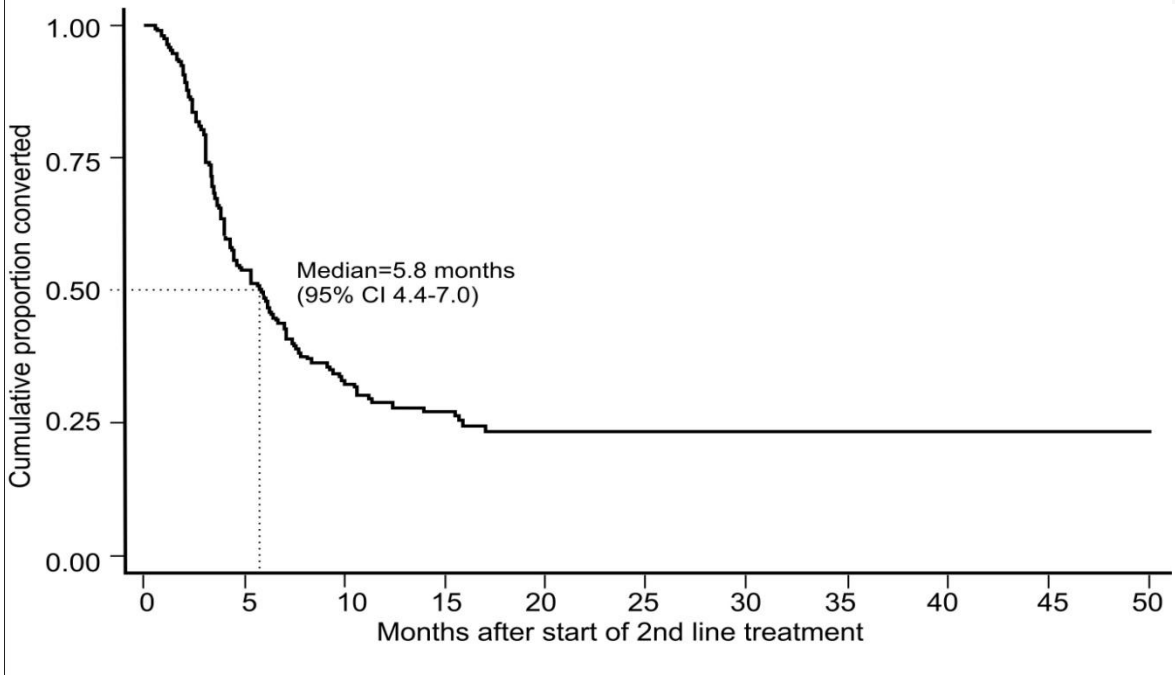


Figure 2B. Sputum conversion in MDR TB patients by sex (n=195)

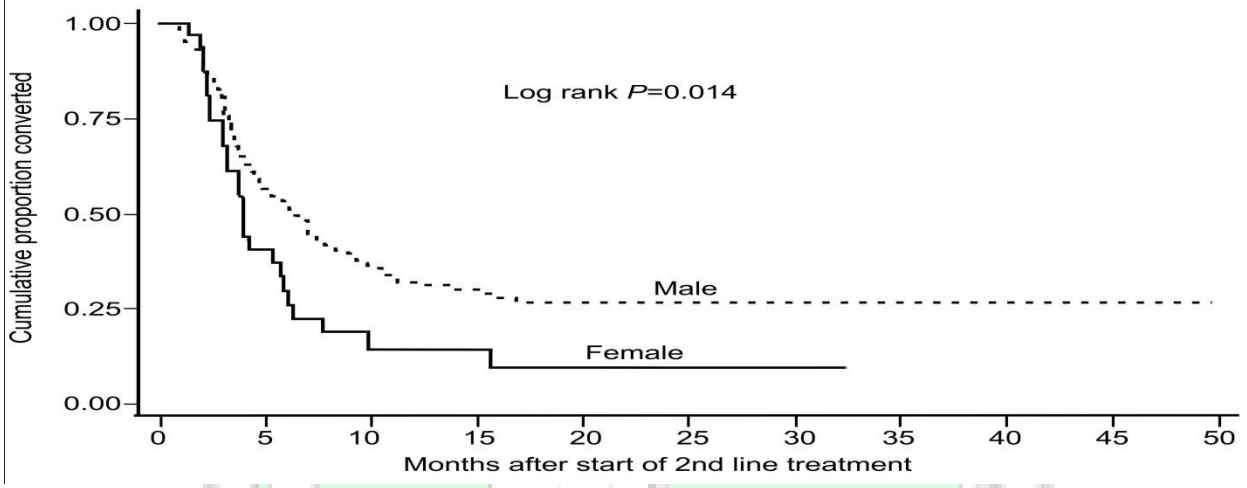


Figure 2C. Sputum conversion in MDR TB patients by ofloxacin resistance (n=161)

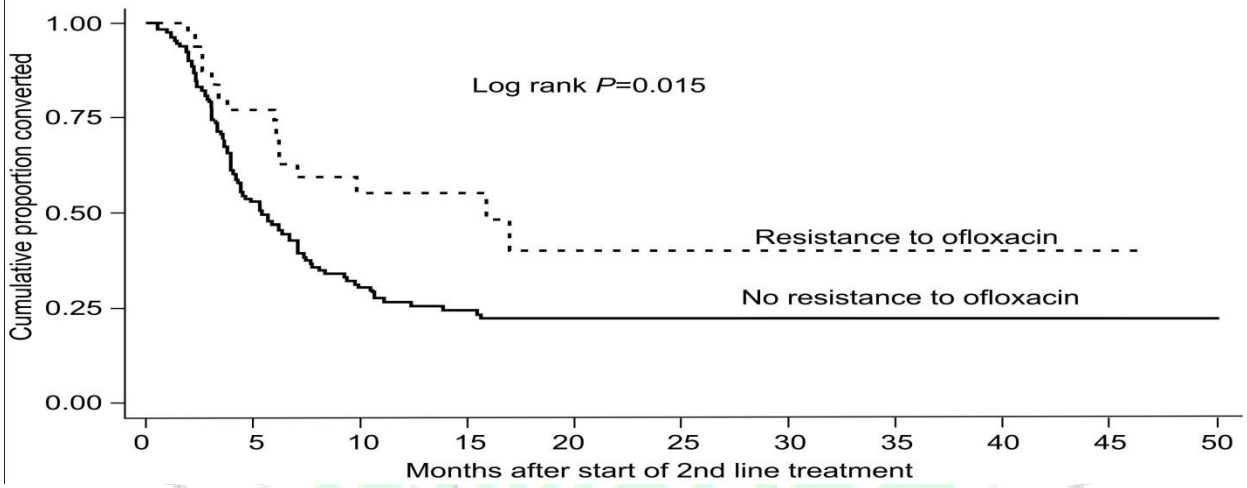
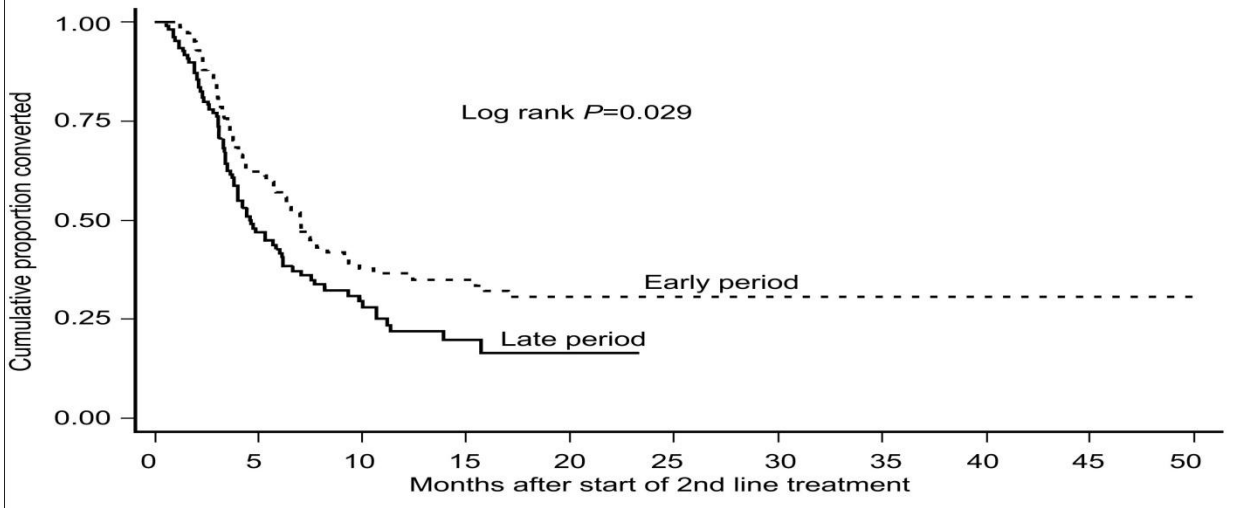


Figure 2D. Sputum conversion in MDR TB patients by period of enrollment (n=195)



Discussion

A total of 68.7% of MDR TB patients that enrolled into second-line treatment achieved sputum conversion. Half of all MDR TB patients converted within 5.8 months. This is about six times as long as for regular TB (Guller et al., 2007; Fortún et al., 2007; Singla et al., 2005). Among these who converted the median time to conversion was 3.8 months.

The variables male sex, colony count at initial culture, number of drugs resistant at initiation of treatment, TB strains resistant to ofloxacin, ethambutol and streptomycin and XDR TB were all associated with delayed sputum conversion in univariate survival analysis. In multivariate Cox regression analysis the variables male sex, TB strains resistant to ofloxacin, and period of enrollment into treatment program were independent risk factors for longer time to sputum conversion.

The strengths of study were close monitoring of patients, high validity of laboratory results due to existing internal and external quality control measures and comparatively high power due to the large sample size.

The main limitation was lack of information on other possible risk factors for delayed sputum conversion, such as cavitations, HIV status, nutrition status, smoking, and other concomitant diseases. Another possible limitation was some selection bias, where subjects with missing values for variables were systematically different from cases where the data were not missing. This introduced some selection bias, since the subjects with missing information on resistance of second-line drugs were mainly patients with early sputum conversion, who responded to the treatment rapidly and providing no time to conduct a culture growth for DST. It is more likely that early convertors are those without second-line drug resistance, which would shift our study estimations towards the null.

Mean time to sputum conversion observed in the Armenian MDR program (175 days) is longer than the mean time for the Latvian MDR treatment program (84 days) reported from the patients for the year 2000 9 (Holtz et al., 2006) but is similar to that reported in a recent study in Karachi, Pakistan (196 days) (Qazi et al., 2011).

Observed difference with Latvia study in time to conversion could be explained in major part by the high prevalence of second-line drug resistance: 15.6% of Armenian patients at initiation of treatment already had resistance to ofloxacin, while only 3.6% of patients in Latvia had ofloxacin resistance. Another possible reason might be the difference in laboratory methods used to produce mycobacterial culture: the Latvian study used solid media for culture, while Armenia as well as Pakistan used BACTEC MGIT 960 system, which is characterized by a higher recovery of mycobacteria from clinical specimens (Tortoli et al., 1999; Hanna et al. 1999).

In our study male sex emerged as a significant risk factor, even after controlling for other variables. The reasons for this require further investigation. One explanation might be that women have better adherence to treatment. Another reason could be confounding effect due to smoking (Kolappan et Gopi 2002).

Unlike the Latvian and Pakistan studies, we found a very strong association between ofloxacin resistance and time to sputum conversion. This was expected finding as fluoroquinolones are the most potent second line anti-TB drugs with a fast sterilizing effect (Johnston et al., 2009; Yew at al., 2003; Maranetra 1999; Caminero 2006).

The reason that patients in the later cohorts with no substantive change in treatment regimen had better conversion rate and converted faster than patients in the early cohorts is encouraging and may be explained in several ways: earlier identification of second-line drug-resistant cases, earlier administration of individually tailored regimen, or recruitment of new MDR patients without previous unsuccessful attempted treatment. This is consistent with other MDR programs showing that later cohort's outcomes are likely to be different than earlier cohort outcomes (Cox et al., 2007).

Unlike the studies that established an association between sputum bacillary load and time to conversion, in our study the existing association between colony count in univariate analysis

disappeared after adjustment for ofloxacin resistance. This was because of a strong association observed between the bacillary load and ofloxacin resistance (P=0.005).
Study findings of sputum conversion are true for patients enrolled in Armenia DOTS-Plus and may not be generalizable for the population with different drug susceptibility patterns or demographic profiles of patients.

Conclusion And Recommendations:
The high prevalence of second-line drug resistance in Armenia MDR patients and delayed conversion of sputum reported in our study is worrisome. Ofloxacin resistance dramatically compromises the efficiency of MDR treatment.

The population-at-risk of delayed conversion, males and patients with ofloxacin resistance should be managed with more aggressive treatment regimens from the start of treatment. In addition, more studies are required to assess other possible factors that cause delays in sputum conversion.

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