Journal of Medicine, Physiology and Biophysics
ISSN 2422-8427 An International Peer-reviewed Journal
Vol.49, 2018

Risk Factors for Drug Resistance-Tuberculosis Among Tuberculosis Cases in Dire Dawa Administration, Ethiopia: Case Control Study

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*This Study was sponsored by TRAC-Ethiopia

Abstract

Background: The 2011 world health organization global tuberculosis report estimated the presence of 650,000 cases of multi-drug resistance tuberculosis among the world's 12.0 million prevalent cases of tuberculosis. Drug-resistant tuberculosis is a man-made problem, largely being the consequence of human error as a result of individual or combination of factors related to management of drug supply, patient management, prescription of chemotherapy, and patient adherence.

Objective: To assess the risk factors associated with drug resistant tuberculosis among tuberculosis cases in Dire Dawa administration council from June to September 2014..

Methods: A health facility based unmatched case control study design was conducted. All diagnosed drug resistant tuberculosis were taken as cases and randomly selected sensitive TB cases were considered as controls. The sample size was 270 (216 for control and 54 for cases) with case to control ratio 1:4, using Epi Info V.6. Finally, data was collected by pre tested questionnaire and coded, edited, entered by Epi Info version 6.0 and analyzed by using SPSS version 16.0. Univariate, bivariate analysis, chi- square test and multivariable logistic analysis were conducted with consideration of P value < 0.05 with 95% CI.

Result: In multi logistic regression, three variables; unemployment, pre-treatment for TB and unsuccessful treatment outcome were found to fit the model. . That is, subjects treated before for TB were 190.7 times more likely to develop DR-TB than counterpart AOR=190.7 with 95% CI (14.53, 2502), unemployed subjects were 2.83 times more likely at risk of DR-TB than employed AOR=2.83 with 95% CI (1.02, 7.86) & those who were unsuccessfully treated were 343 times more likely at risk of DR-TB than with successful treatment outcome AOR=343 with 95% CI (29.9, 3985)

Conclusion: Previous history of treatment, unemployment and unsuccessful treatment outcome were significant risk factor associated with DR-TB. Therefore, DOTS program should be strengthened to increase patient adherence for successful treatment of patients.

Keywords: TB, drug resistance TB, Risk-factor

1. INTRODUCTION

Drug-Resistant *Tuberculosis* (DR-TB) is a man-made problem, largely being the consequence of human error as a result of individual or combination of factors related to management of drug supply, patient management, prescription of chemotherapy, and patient adherence[(1)].The increasing prevalence of infection with drug-resistant Mycobacterium tuberculosis represents a global public health emergency. [(4).]The 2011 WHO Global TB Report estimated the presence of 650,000 cases of MDR-TB among the world's 12.0 million prevalent cases of TB. [(4).] Ethiopia is among 27 high MDR-TB burden countries that carry 87% of the total global burden and one of the four countries in Africa (i.e. South Africa, Nigeria and DRC). The 2003-2005 drug resistance TB survey result showed, 1.6% of new cases and 11.8 % of retreatment cases in Ethiopia were resistance to isoniazid and ri-fampicin, (MDR-TB) (4). Ethiopian MDR-TB implementation frame work developed through adaption of Stop TB Strategy. It addresses TB/HIV and MDR-TB, strengthening of health systems, engagement of community and all care providers.

Moreover, the strategy also entails operational research, in addition to DOTS and DOTS-plus. Each of the six components of the strategy has an important contribution to the success of the program [(4).] There are several reasons for emerging DR-TB in developing countries lack the laboratory facilities for the diagnosis of MDR-TB and the clinical expertise and chemotherapeutic agents for its management. Although effective second-line drugs are available, they are expensive and treatment takes 18– 24 months [(7).] Hence, there has been a recent shift in the international attitude towards dealing with the MDR-TB burden. The goal now is to provide universal access to

diagnosis and treatment of MDR-TB by the year 2015 (similar to the goal of universal access to ART) [6].

The ultimate strategy to control drug-resistant tuberculosis is one that implements comprehensive approach incorporating treatment of drug-resistant tuberculosis based upon principles closely related to those of the general DOTS strategy for TB control: sustained political commitment; a rational case-finding strategy including accurate, timely diagnosis through quality assured culture and DST; appropriate treatment strategies that use second-line drugs under proper case management conditions; uninterrupted supply of quality-assured anti-tuberculosis drugs; standardized recording and reporting system [4].Coming to Dire Dawa administration, 22 and 34 in 2005EFY and 2006 EFY respectively, which make the total all number of MDR-TB currently on treatment 56. This study identified the factors associated with DR-TB and used for policy makers, program planners and service providers to improve TB services

2. The Research Question and Hypotheses

2.1 Research Questions

- What are the major risk factors associated with drug resistance among TB cases in Dire Dawa Administration?

2.2 Hypothesis

- Socio demographic factors of the patients have no effect on development of DR-TB.

2.3 Objective

The objective of this study was to assess risk factors associated with DR-TB among TB cases in Dire Dawa administration from June to September 2014.

3. Methods

Study was conducted in Dire Dawa administration located in eastern part of Ethiopia from June to September 2014.The study design was health facilities based unmatched case control.

Source population of the study was all forms of TB cases and study population was all diagnosed DR-TB for cases (patients with laboratory confirmed DR-TB at least for Rifampicin and randomly selected sensitive TB cases for controls (all sensitive TB patients those who completed treatment during data collection period) were included in the study.

3.1 Inclusion and Exclusion Criteria

3.1.1 Inclusion Criteria

All TB cases age greater than 10 years old were included in the study because their treatment protocols were different from that of less than ten years according to the compressive TBL and TB/HIV Ethiopia treatment guideline 2013.

3.1.2 Exclusion Criteria

Critically ill TB patients/those who couldn't respond were excluded.

3.2 Sample Size Determination and Sampling Techniques

Double population proportion formula was used for sample size calculation by using Epi Info version 6 by considering household contact as predictor variable(OR=5)(22), 4:1 control to case ratio, 4.4% percentage exposure among controls ; 80% power and 95% confidence level. The sample size was 270(216 controls and 54 cases) including 10% non-response rates. A systematic random sampling technique was used to select control (those who were on sensitive Tb treatment and who completed treatment within data collection period) and DR-TB patients diagnosed at health facilities in the administration. The sampling frame was unit TB register.

3.3 Study variables

The independent variables include socio demographic variables, treatment category/regimen, adherence, co-infection (HIV/AIDS), treatment supporter and household contact. And the dependent variable for this study was DR-TB.

3.4 Data Collection Instrument/tool

Inter viewer administered structured questionnaire and check list were used to collect data

3.5 Data collection Procedure

Data was collected by trained Bsc Nurse and public health professionals.

3.6 Data Quality control
Data collectors and supervisors trained; tools were pre tested on 5% sample size and the collected data were submitted to the supervisors on daily based and feedback were given on the next day morning

3.7 Data Analysis
The data were coded and entered into the data sheet using EPI info version 6.0, then exported to SPSS version 16.0 for further analysis. All continuous variables were described using mean and standard deviation and frequency (%) for categorical data. For categorical data chi square was used and bi-variate analysis and multivariate logistic regression were applied to determine predictor variables on the outcome variables at 95% CI

3.8 Ethical consideration
Proposal was approved by Institution Health Research Ethics Review Committee (IHRERC) of Collage of Health and Medical Sciences, Haramaya University and cooperation letter was obtained from Dire Dawa regional Health Bureau.

4. Result
A total of 265(53 cases and 212 control) were participated in the study which makes a response rate of 98%. Majority of study participants were males among cases and controls 36(67.9%) and 122(57.5%) respectively. The mean age was 31.1 (SD = 13.0) years for DR-TB cases and 32.0 (SD = 16.5) years for sensitive TB controls .Majority, 29(54.7%), were single among cases and 94(44.5%) were single among controls. (Table1).

4.1 Background Information
Table 1: The Background Information of the Participants

Characteristics	Cases(N=53)		Controls (N=212)	
	Number	Percentage	Number	Percentage
Sex				
Male	36	67.9	122	57.5
Female	17	32.1	90	42.5
Total	**53**	**100**	**212**	**100**
Educational status				
Unable to read and write	5	9.4	59	27.8
Read and write only	5	9.4	13	6.1
1-8 grades	23	43.4	67	31.6
9-10 grades	6	11.3	36	17
Greater 10^{th} grade	11	20.8	22	10.4
Diploma	2	3.8	10	4.7
Degree and above	1	1.9	5	2.4
Total	**53**	**100**	**212**	**100**
Marital status				
Single	29	54.7	94	44.5
Married	16	30.2	86	40.8
Widowed	2	3.8	12	5.7
Divorced(legally)	4	7.5	10	4.7
Separated (not legally	2	3.8	9	4.3
Total	**53**	**100**	**211**	**100**
Religion				
Muslim	24	45.3	138	65.1
Orthodox	25	47.2	68	32.1
Protestant	3	5.7	6	2.8
Catholic	1	1.9	0	0
Total	**53**	**100.1**	**212**	**100**

From the Table above, the percentage of the male participants (68 %) is almost as twice as that of the female participants (32%) for cases whereas, for control participants, the number of male and female participants was less different gender wise with 57.5 % and 42.5 % respectively. The percentage of participants in terms of their educational status, was highest for the primary education (43.4) followed by grade 10^{th} complete for cases, and the same for the highest and followed by illiterate for (31.6%) and (27.8 %) respectively. Generally, most of the participants were illiterate or only at primary education.

Marital wise, more of the participants for both cases and control were single followed by divorced parents.

Religion wise, more cases belong to Orthodox (47.2) and more controls belong to Muslims (65.1%). Generally, more of the participants came from Muslim and Orthodox religions followed by insignificant portion of Protestant and Catholic religions.

4.2 DR-TB Conditions for Cases and Controls

Table 2: Drug Resistant and Sensitive TB related conditions for Cases and Controls in Dire Dawa, 2014

Characteristics	Cases(N=53)		Controls (N=212)	
	Number	Percentage	Number	Percentage
Treated for Tb before				
Yes	50	94.3	30	14.2
No	3	5.7	182	85.8
Total	53	100	212	100
Contact person treated in HH				
Yes	9	17	36	17
No	24	45.3	158	74.5
I don't know	20	37.7	18	8.5
Total	53	100	212	100
Ever interrupt/stop TB treatment				
Yes	12	22.6	7	3.3
No	41	77.4	205	96.7
Total	53	100	212	100
Length of Interruption				
<=10 days	4	33.3	6	85.7
>10 days	8	66.7	1	14.3
Total	12	100	7	100
Change Residence during TB Treatment				
Yes	9	17	25	11.8
No	44	83	187	88.2
Total	53	100	212	100
Smoke while TB RX				
Yes	5	9.4	13	6.1
No	48	90.6	199	93.9
Total	53	100	212	100
Miss TB treatment due to smoking				
Yes	2	40	1	7.7
No	3	60	12	92.3
Total	5	100	13	100
Ever chewed chat				
Yes	14	26.4	52	24.5
No	39	73.6	160	75.5
Total	53	100	212	100
Miss TB treatment due to chewing chat				
Yes	1	7.1	4	7.7
No	13	92.9	48	92.3
Total	14	100	52	100
Drink alcohol while TB RX				
Yes	10	18.9	21	9.9
No	43	81.1	191	90.1
Total	53	100	212	100
Miss TB RX doe to alcohol use				
Yes	1 1	10	2	9.5
No	9	90	19	90.5
Total	9	90	19	90.5

4.3 Associated Factors for drug resistant Tuberculosis

Based on the binary logistic regression, the variables associated with drug resistant were treated for TB before COR =101 with 95% CI (29.6, 345) and unsuccessful treatment outcome COR=89.3, CI (39.9, 228.5) , See table

3.

Table 3 Associated factors by Binary logistic regression in Dire Dawa 2014

Characteristics	Cases(N=53)	Controls (N=212)	COR at 95%CI
	Number	Number	
Sex			
Male	36	122	1.56(0.83,2.95)
Female	17	90	1
Educational level			
Illiterate	10	72	2.21(1.1,4.7)
Literate	43	140	1
Age in years			
<=45	43	174	1.16(0.53,2.51)
>45	10	35	1
Marital status			
Single/divorced/widowed	37	125	1.59(0.83,3.0)
Married	16	86	1
Residence			
Urban	49	175	2.6(0.88,7.62)
Rural	4	35	1
Occupation			
Employed (governmental and private)	7	57	1
unemployed	46	155	2.42(1.03,5.7)
Treated for TB before			
Yes	50	30	101(29.6,345)
No	3	182	1
Contact person treated in HH/family			
Yes	9	36	1.65(0.71, 3.84)
No	24	158	1
Ever interrupt/stop TB treatment			
Yes	12	7	8.6(3.2, 23.2)
No	41	205	1
For how long you interrupt/stop TB RX			
<=10 days	4	6	0.08(0.007,0.95)
>10days	8	2	1
Frequency of drug provision during the intensive phase			
Daily	41	188	0.43(0.20,0.94)
Weekly	12	24	1
Have treatment supporter			
Yes	51	147	1
No	2	54	9.37(2.20,39.8)
Your treatment supporter			
Health extension worker	2	14	1.65(0.35,7.83)
Neighbor	26	24	0.22(0.11, 0.45)
From family members	21	89	1
Diagnosed for chronic disease/illness (s)			
No/I don't know	22	147	1
Yes (DM,HTN,HIV/AIDS, others)	31	65	0.73(0.19, 2.8)
HIV/AIDs Status of the patient			
Reactive	10	7	1.3(0.6,2.85)
Non-reactive	43	205	1
Category of the patient			
New	10	176	1
Retreatment	43	36	21(9.7,45.7)
Intensive phase drug			
RHZE	12	119	1
RHZES	41	3	52(22.3,122.8)
Drug given during continuous phase			
RHE	40	9	69.4(27.8,173.4)
RH	13	203	1
Patients treatment out come			
Unsuccessful treatment outcome	44	11	89.3(39.9,228.5)
Successful treatment outcome	9	201	1

4.4 Determinants of drug-resistant tuberculosis

In multi logistic regression two variables were remain in the modal that is study subjects treated before for TB were 190.7 times more likely to develop drug resistance TB than counterpart AOR=190.7 with 95% CI (14.53, 2502) and those have unsuccessful treatment outcome were 343 times more likely to develop drug resistance TB than those have successful treatment outcome AOR=343 with 95% CI (29.9, 3985) .See table 4

Tabl 4. Determinants of Drug-Resistant Tuberculosis by Logistic Regression Model

Characteristics	Cases(N=5)	Controls (N=212)	COR at 95%CI	AOR at 95%CI
	Number	Number		
Education				
Illiterate	10	72	2.21(1.1,4.7)	0.53(0.21,1.38)
Literate	43	140	1	1
Age in years				
<=45	43	174	1.16(0.53,2.51)	1.03(0.31,3.38)
>45	10	35	1	1
Occupation				
Employed (private and gov't)	7	57	1	1
Unemployed	46	155	2.42(1.03,5.7)	2.83(1.02,7.86)
Treated for TB before				
Yes	50	30	101(29.6,345)	190.7 (14.53, 2502)
No	3	182	1	1
Contact person treated in HH/family				
Yes	9	36	1.65(0.71, 3.84)	2.5(0.64,9.76)
No	24	158	1	1
Ever interrupt/stop TB treatment				
Yes	12	7	8.6(3.2, 23.2)	2.25 (0.38,13.13)
No	41	205	1	1
Have treatment supporter				
Yes	51	147	1	1
No	2	54	9.37(2.20,39.8)	3.85(0.12,1.2)
HIV/AIDs Status of the patient				
Reactive	10	7	1.3(0.6,2.85)	1.36(0.14,13.5)
Non-reactive	43	205	1	1
Category of the patient				
New	10	176	1	1
Retreatment	43	36	21(9.7,45.7)	2.63(0.43,16.04)
Unsuccessful treatment outcome	44	11	89.3(39.9,228.5)	343(24,398.5)
Successful treatment outcome	9	201	1	1

5. DISCUSSION

A case control study with one to four numbers of cases and controls (1:4) was conducted by recruiting a total of 265 study subjects (53 drug resistant TB cases and 212 sensitive TB controls) to determine the risk factors associated with development of drug resistant TB. From socio-economic demographic variables, the unemployment status remain in the model as risk factor for the drug resistant TB (DR-TN) in which unemployed individuals among all cases account for 86.8 % and have 2.83 more risk of developing DR TB with AOR=2.83 at 95%CI (1.02,7.86) which was similar with study done in Namibia [18]. Even if different studies undertaken in Nepal, India and Namibia, shows the association of age with DRTB [10,12,18], our study didn't show statistical significant but more than half (58.5%) of cases lie in age group of 10-29 years that was similar with study from Turkey as no age difference detected for risk factors [14]. Concerning sex, in many epidemiological studies such as study undertaken in Iran, Belarus, Addis Ababa [18, 21, 22] showed that being male was a risk factor for developing DRTB than female counterpart but in India being female was a risk factor [13] but no association found between sex and drug resistant TB in our study even majority of DRTB cases 67.9% were male which the same with study undertaken in Nigeria, Turkey [13,14]. In addition to these, there were no association between education level and DRTB which was similar with finding from Belarus [21].No difference detected in marital status which in line with result from Turkey and Addis Ababa [14, 22]. As we can see, the risk of developing DR-TB among previously treated individuals was 190.7 times increased than counterpart at 95%

(14.53, 2502). This finding is similar with different study done in Nepal, India, Turkey, Nepal, Namibia and Iran [10.13-14, 16-18]. An individual using category II regimen were 4.9 times high risk to develop DRTB that was similar with study done in Addis Ababa [22]. House hold contact was not associated with DRTB in our study even if it was a risk factor for DRTB in different studies like in Namibia and Addis Ababa [17, 22]. HIV/AIDS is not statistical significant in our study that was in line with study done in India and Addis Ababa [13,12] but in study done in Namibia [17] HIV/AIDS increase the risk of developing DRTB. The factors related to clients that we assessed were alcohol use that was18.9% among cases and 9.9% among controls which is not significantly related to DR TB in our study even if it is one predictor in other studies under taken in the Nepal, Russia and Belarus ([16, 20, 21]).

Smoking tobacco, among smokers 9.5% from cases and 6.1% from controls, was not significantly related to DRTB in our finding that contradicts the finding from Belarus that show significant association [21]. TB treatment interruption or missing dose was 22.6% and 3.3% of cases and controls respectively. That was not statistically significant with AOR=2.25, 95% CI (0.38, 13.13) which contradicted studies under taken in the Europe meta-analysis, Russia & Addis Ababa (19, 20, 22). The factors related to health care providers of allowing clients to take the drugs by themselves among cases, 22.6% and 19.8% of controls were not significantly related to DRTB that contradicted the study done in Paris, Thailand and Addis Ababa [11, 15, 22].

6. CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

- ✓ Unemployment, treated before for TB (previous history of treatment) and unsuccessful treatment outcome were significantly related with drug resistant TB
- ✓ House hold contact, treatment supporter, HIV/AIDS status were not significantly related with DRTB
- ✓ Drinking alcohol, cigarette smoking , chat chewing and TB treatment interruption from client's side and allowing clients to take the TB drugs by themselves from health care provided corner were not significantly related to DRTB

6.2 Recommendation

- DOTS program should be strengthened to increase patient adherence for successful treatment of patients.
- More researches should be further conducted to increase the body of knowledge over this area Seminars, Symposiums

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