PREDICTORS OF TREATMENT INTERRUPTION IN PULMONARY TUBERCULOSIS PATIENTS

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ABSTRACT

Introduction: Tuberculosis (TB) is a common and deadly infectious disease caused by mycobacterium, mainly mycobacterium tuberculosis.[1] The World Health Organization declared TB a global health emergency in 1993.[2] This is a cross sectional descriptive study.

Objective: To identify factors predicting treatment interruption in pulmonary tuberculosis patients under DOTS (Directly Observed Treatment Short Course) strategy in District Lahore. It is conducted on 421 pulmonary tuberculosis patients under DOTS, in district Lahore, Pakistan in 2006 – 07.

Results: At the end of the treatment period, the treatment interrupters were 31 / 421 (7.4%). Among them 25 / 421 (5.9%) were defaulters, while 6 / 421 (1.4%) were non-compliers. Analysis showed a significantly increased risk of treatment interruption among those who need to travel in order to get medicine ($p < 0.0001$), those who need to travel a distance of more than 30 minutes walk to get medicine ($p < 0.0001$), those who occasionally need to buy medicine ($p = 0.024$) and those patients who were directly observed by health care provider ($p < 0.0001$).

Conclusion: The issue of treatment interruption in tuberculosis patients and the factors identified in the study, need to be addressed, so the compliance can be improved.

Key words: tuberculosis, treatment interruption, non-compliance, predictors of default, Default rate, DOTS.

INTRODUCTION

Tuberculosis (TB) is a common and deadly infectious disease caused by mycobacterium, mainly mycobacterium tuberculosis.[1] The World Health Organization declared TB a global health emergency in 1993.[2] "TB Anywhere is Everywhere", the theme for World TB Day 2007, emphasises that Tuberculosis is still a global emergency largely due to its mode of transmission. Pulmonary TB remained the most common form of active disease. There were an estimated 8.8 million new cases in 2003, 7.4 million in Asia and sub-Saharan Africa. A total of 1.6 million people died of TB, including 195,000 patients infected with HIV.[3] Tuberculosis constitutes the third most important cause of death and disability among infectious diseases.[4] The World Health Assembly (WHA), in 1991, pledged countries to achieve detection of at least 70% of estimated infectious TB cases, sputum smear positive (SS+) and to cure 85% of them by the year 2000, but these targets were not achieved until 2005.[5] World leaders formulate the eight Mellennium Development Goals (MDGs), in which the goal to halt, and begin to reverse, the global incidence of TB by 2015 was agreed upon.[6] Stop TB Partnership in 1998 and Global Fund (GFATM) in 2001 represented significant developments, in the fight against TB.[7] In 2006, WHO launched the new Stop TB strategy, the core of this strategy is directly observed treatment short course (DOTS), which is the TB control approach launched by WHO in 1993.[8]

There are 22 High Burden Countries (HBCs), these countries account for more than half of the world's population and approximately 80% of the global TB burden.[9] According to the WHO report 2007, Pakistan ranks 6th amongst the high burden EMR countries, where the incidence of pulmonary TB cases in 2005 was[8] and prevalence 297 per 100,000 population, while mortality was 37 per 100,000 population. DOTS treatment success rate in SS+ cases in 2004 cohort was 82% against the target of 85%.[10] After that the DOTS treatment success rate has improved from 79 to 88 percent between 2003 and the 2006 cohort. The improvement in case detection and the number of TB cases reported due to efforts of involving private practitioners and community volunteers in identifying and referring TB suspects, along with the help of general pu-

blic in case finding.[11] To improve adherence to anti-tuberculosis treatment many methods are in practice like, inbuilt monitoring system[12] pill counts, urine tests, hospitalisation, combination tablets, blister packs, and supervised therapy.[13,14] In Pakistan directly observed therapy (DOTS) was introduced nationwide to promote compliance. Defaulting from tuberculosis treatment remains a major challenge in the developing world for tuberculosis control programs. There is increased risk of drug resistance, relapse, death, and prolonged infectiousness among defaulters. The present study will provide an evidence base for future policies and plans for TB control. The objective of the study is to identify predictors of treatment interruption in pulmonary tuberculosis patients under DOTS (Directly Observed Treatment Short Course) strategy in District Lahore, Pakistan.

METHOD

Study was conducted in district Lahore in province of Punjab, Pakistan. DOTS strategy is implemented in Punjab through the Provincial Tuberculosis Control Program of Pakistan (PTP).

Eligibility Criteria

1. All new cases of Pulmonary Tuberculosis registered at any of the diagnostic centres of Punjab TB Control Program in district Lahore.
2. Patients who started DOTS therapy during the period from July 01, 2006 to Jan. 31, 2007.
3. Patients residing in district Lahore.

The study design was Cross – sectional descriptive. Eligible TB patients were traced and approached throughout the district and were interviewed at home, regarding the determinants / predictors of treatment interruption (non-compliance and defaulting). At the end of their treatment period, the treatment success was assessed on another questionnaire. The study sample collected was 421 eligible pulmonary TB patients. All patients were included in the study until our sample size was completed. Pre-tested structured questionnaires were administered. Data collection was done in two phases. In first phase, the addresses traced and patients identified and the information on the predictors / factors that could potentially predict default and non-compliance was collected. These predictors included demographic, socio-cultural and behavioral factors and also the Direct observation (DO) component of the treatment during intensive phase. In the second phase at the end of treatment, their adherence to treatment was determined and sputum smear testing was done. The default rate is defined as new pulmonary TB patients receiving treatment for at least four weeks and whose treatment is interrupted for more than or equal to two months. Non-compliers were those patients whose interruption was of less than 2 months. Ethical clearance was obtained from local Institutional Review Board. Written Informed consent was obtained from the study participants, while in case of minor the parents gave the consent. The consent form was translated in local language. The defaulters when detected were encouraged to continue medicine.

RESULTS

Treatment success was assessed in 421 patients enrolled in the study. The patients who never stopped medicine were 390 (92.6%) and those who interrupted the treatment were 31 (7.4%). Among these 31 (7.4%) subjects 25 (80.64%) were Defaulters (treatment interruption for > = 2 months), while 6 (19.35%) were Non-compliers (treatment interruption for less than 2 months). The default rate was 3.9% (25 / 421).

The distribution of study population regarding the potential risk factors for non-compliance / default is given in Table 1. The subjects were in the ages from 2 to 85 years with the mean age of 33.81, SD ± 17.946 and 95% CI 32.13 – 35.48 using one sample t-test. Among the 421 patients, males were 177 / 421 (42.0%) and females 244 / 421 (58.0%). Among female patients the mean age was 31.13 with SD ± 16.871, while in males mean age was 37.49 with SD ± 17.719. in these 61.8% patients were married, 36.3% were unmarried and 1.9% faced death of spouse. 233 / 421 (55.3%) were illiterate, including 55.79% females and 44.21% males. In the category of literates and under matric (grade 10) there were 107 / 188 (25.4%) patients. In Matric and Post-matric category there were 81 / 188 (19.2%) patients. On average there were 2.35 living rooms in the residences of the subjects. There were 102 / 421 (24.7%) subjects having just one living room in their houses, while 42% had 2 living rooms and rest had 3 or more living rooms. Family size on average was 6.79. Only 44.1% subjects had a family size of 5 or less than 5, while 55.9% had a family size of more than 5, out of which 28% had a family size of 10 or more than 10. Average family income in PKR per month was 5037.02 while average per – day, per – capita income was PKR – 28.37 with a SD ± 19.05 and a minimum of PKR – 3. Unfortunately 403 / 421 (95.7%) subjects and their families were living below the poverty line of 1$ a day (per capita). There were 290 (68.9%) patients in the non-working group among which majority (78.96%) were female subjects were males. According to the number of earning members in the families of 421 subjects, we found that 286 / 421 (71.9%) subjects had just one earning member, while 23 / 421 (5.93%) families had no earning hand. There were 26.1% families with 2 or more than 2 earning members.

Table 1: *Distribution of study population regarding the potential risk factors for non-compliance.*

Variables	*Sub-categories*	*Frequency*	*Percentage*
Gender	Females	244	58
	Males	177	42
	Total	421	100
Age	< = 25 years	162	38.5
	> 25 years	259	61.3
	Total	421	100
Marital status	Single	153	36.3
	Ever married	268	63.7
	Total	421	100
Patient Education	Illiterate	233	55.3
	Literate + formal education	188	44.7
	Total	421	100
Occupation	Non-working	290	68.9
	Working	131	31.1
	Total	421	100
Income	Less than a S / capita / day	403	93.7
	= > a $ / capita / day	18	4.3
	Total	421	100
Traveling for Medicine	Need to travel	173	41
	Don't need to travel	248	39
	Total	421	100
Traveling Distance	> 30 minutes walk	106	62
	= < 30 minutes walk	66	38
	Total	173	100
Feel stigmatized	Yes	225	53.4
	No	196	46.6
	Total	421	100
Apprehensions / Myths	Yes	87	20.7
	No	334	79.3
	Total	421	100
Need to buy medicine sometimes	Yes	111	26.4
	No	310	73.6
	Total	421	100
Changes done to diet due to TB	Yes	357	84.8

Variables	*Sub-categories*	*Frequency*	*Percentage*
	No	64	15.2
	Total	421	100
Direct Observation	No	123	29.2
	Yes	298	70.8
	Total	421	100
Patient opinion about continuing medicine after intensive phase	No need to continue	13	03
	Should continue	408	97
	Total	421	100
Type of treatment supporter	By health care provider	58	19.5
	By family / community members	240	80.5
	Total	298	100

Table 2: *Treatment outcome in relation to potential risk factors for non-compliance.*

			Treatment interrupters		
Variables	*Sub-categories*	*Compliers*	*Defaulters + Non-compliers*	*Defaulters*	*Non-compliers*
Gender	Females	221 (56.6%)	23 (74.1%)	17 (68%)	06 (100%)
	Males	169 (43.3%)	8 (23.8%)	08 (32%)	0
	Total	390 (100%)	31 (100%)	25 (100%)	06 (100%)
	RR=2.08 (0.95 – 4.55)** ARI*** = 0.049 (0.001 – 0.097) OR**** = 2.199. Chi-square = 2.937 with p = 0.08*				
Age	< = 25 years	150 (38.4%)	12 (38.7%)	07 (28%)	05 (83.3%)
	> 25 years	240 (61.5%)	19 (61.2%)	18 (7.2%)	01 (16.7%)
	Total	390 (100%)	31 (100%)	25 (100%)	06 (100%)
	PR = 1.01 (0.50 – 2.02) ARI = 0.001 (0.03 – 0.052)				
Marital status	Single	141 (36.2%)	12 (38.7%)	07 (28%)	05 (83.3%)
	Ever married	249 (63.85%)	19 (61.3%)	18 (72%)	01 (16.7%)
	Total	390 (100%)	31 (100%)	25 (100%)	06 (100%)
	RR = 1.106 (0.55 – 2.21) ARI = 0.008 (-0.045 – 0.06)				
Patient Education	Illiterate	218 (55.9%)	15 (48.4%)	12 (48%)	03 (50%)
	Literate + formal education	172 (44.1%)	16 (31.6%)	13 (52%)	03 (50%)
	Total	390 (100%)	31 (100%)	25 (100%)	06 (100%)
	*RR = 0.73 (0.38 – 1.49) ARR**** = 0.021 (-0.03 – 0.072)*				
Occupation	Non-working	266 (68.2%)	24 (77%)	18 (72%)	06 (100%)
	Working	124 (31.8%)	7 (23%)	07 (28%)	0
	Total	390 (100%)	31 (100%)	25 (100%)	06 (100%)

	R = 1.55 (0.68 – 3.50) ARI = 0.029 (-0.021 – 0.079)				
Income	Less than a $ / capita / day	373 (95.6%)	30 (96.8%)	24 (96%)	06 (100%)
	= > a $ / capita / day	17 (4.4%)	01 (3.2%)	01 (4%)	0 (%)
	Total	390 (100%)	31 (100%)	25 (100%)	06 (100%)
	PR = 1.34 (0.193 – 9.284) ARI = 0.019 (-0.09 – 0.128)				
Traveling for Medical	Need to travel	144 (36.9%)	29 (93.5%)	23 (92%)	06 (100%)
	Don't need to travel	246 (63.1%)	02 (6.5%)	02 (8%)	0 (%)
	Total	390 (100%)	31 (100%)	25 (100%)	06 (100%)
	RR = 20.78 (5.026 – 85.97) ARI = 0.16 (0.103 – 0.216) OR = 24.77 (5.82 – 105.3), Chi-square = 35.73 with p < 0.0001				
Traveling Distance	> 30 minutes walk	88 (61.1%)	18 (62%)	15 (65.2%)	03 (50%)
	= < 30 minutes walk	56 (38.9%)	11 (38%)	08 (34.8%)	03 (50%)
	Total	144 (100%)	29 (100%)	23 (100%)	06 (100%)
	RR = 4.387 (2.2238 -8.637) ARI = 0.138 (0.06 – 0.215) OR = 5.12 (2.41 – 10.88), Chi-square = 19.37 with p < 0.0001				
Feel stigmatized	Yes	209 (53.6%)	16 (51.6%)	13 (52%)	03 (50%)
	No	181 (46.4%)	15 (48.4%)	12 (48%)	03 (50%)
	Total	390 (100%)	31 (100%)	25 (100%)	06 (100%)
	RR = 0.92 (0.47 – 1.83) ARR = 0.005 (-0.045 – 0.056)				
Apprehensions / Myths	Yes	77 (19.7%)	10 (32.3%)	09 (36%)	01 (16.7%)
	No	313 (80.3%)	21 (67.7%)	16 (64%)	05 (83.3%)
	Total	390 (100%)	31 (100%)	25 (100%)	06 (100%)
	RR – 1.83 (0.894 – 3.738) ARI – 0.052 (-0.02 – 0.124)				
Need to buy medicine sometimes	Yes	97 (24.9%)	14 (45.2%)	12 (48%)	02 (33.3%)
	No	293 (75.1%)	17 (54.8%)	13 (52%)	04 (66.7%)
	Total	390 (100%)	31 (100%)	25 (100%)	06 (100%)
	RR = 2.3 (1.173 – 4.51) ARI = 0.071 (0.005 – 0.138) OR = 2.488 (1.182 – 5.233), Chi-square = 5.98 with p = 0.024				
Changes done in died due to TB	Yes	330 (84.6%)	27 (87%)	22 (88%)	05 (83.3%)
	No	60 (15.4%)	4 (13%)	03 (12%)	01 (83.3%)
	Total	390 (100%)	31 (100%)	25 (100%)	06 (100%)
	RR = 1.21 (0.438 – 3.342) ARI = 0.013 (-0.052 – 0.078)				
Direct Observation	No	110 (28.2%)	13 (41.9%)	11 (44%)	02 (33.3%)
	Yes	280 (71.8%)	18 (58.1%)	14 (56%)	04 (66.7%)
	Total	390 (100%)	31 (100%)	25 (100%)	06 (100%)
	RR = 1.75 (0.885 – 3.46) ARI = 0.045 (-0.015 – 0.106 OR = 1.83 (0.87 – 3.87), Chi-square = 1.99 with p = 0.15				

Patient opinion about continuing medicine after intensive phase	No need to continue	11 (2.8%)	02 (6.4%)	02 (8%)	0
	Should continue	379 (97.2%)	29 (93.5%)	23 (92%)	06 (100%)
	Total	390 (100%)	31 (100%)	25 (100%)	06 (100%)
	RR = 2.164 (0.577 – 8.121) ARI = 0.083 (-0.115 – 0.28) OR = 2.37 (0.50 – 11.23), Chi-square = 0.343 with p = 0.55				
Type of treatment supporter	By health care provider	44 (15.7%)	14 (77.8%)	11 (78.6%)	03 (75%)
	By family / community members	236 (84.3%)	4 (22.2%)	03 (21.4%)	01 (25%)
	Total	280 (100%)	18 (100%)	14 (100%)	04 (100%)
	RR = 14.383 (4.95 – 42.374) ARI = 0.225 (0.113 – 0.336) OR = 18.77 (5.90 – 59.67), Chi-square = 17.69 with p < 0.0001				

*Relative Risk, **95% confidence interval, ***Absolute Risk Increase, ****Absoulte Risk Reduction, *****Odds ratio

Gender related factors were evaluated and the results showed that 119 / 244 (48.77%) females need to seek permission to go to a treatment center, out of these 48.7% need permission from husband, 47.1% from parents and 4.2% from in – laws, while 51.2% females made decision on their own. The feeling of insecurity was faced by (43.9%) females while travelling alone to the treatment center. To seek advice from a male doctor was difficult for only 28.4% females due to cultural and religious reasons. Daily work load was an issue for 51% female patients. Evaluating the cultural factors showed that 225 / 421 (53.4%) patients felt stigmatised when someone knews about their disease. Concerns about side effects, and queries regarding anti-TB drugs were seen in 86.2% patients. A dietary change was made due to tuberculosis by 357 / 421 (84.8%) patients. Majority (97.9%) of the subjects said that their physician/ health care provider provided them the necessary information about the disease, Pulmonary Tuberculosis. When asked whether or not instructions were provided by the health care provider with respect to timing, duration and dose of anti-tuberculosis medicines, majority (98.1%) answered in affirmation. In 298/421 (70.78%) patients 'direct observation' (DO) was made during intensive phase. In 123 / 421 (29.2%) patients the direct observation of the treatment was not made. Health care providers were responsible for DO in 58 / 298 (19.5%) cases and a family member or a person in the community was responsible for the direct observation in 240 / 298 (80.5%) patients. On questioning about the nature of direct observation 93.62% subjects told that they had been observed until they swallow the medicine.

Treatment completion was assessed by visiting the patients at the end of their treatment period. The patients who never stopped medicine were 390/ 421 (92.6%) and those who interrupted the treatment were 31 / 421 (7.4%). Among these 31 (7.4%) patients, 25 (80.64%) were defaulters (treatment interruption for > = 2 months), while 6 (19.35%) were Non-compliers (treatment interruption < 2 months). The default rate (treatment interruption > = 2 months) comes out to be 5.94%. Treatment success was confirmed using sputum smear testing. Out of 362 / 421 (85.98%) tested, 91.7% were found to be negative. In 18 / 31 (58%) patients, treatment interruption occurred during continuation phase.

Analysis

The analysis showed a significantly increased risk of treatment interruption among those who need to travel in order to get medicine *(RR = 20.78 CI 5.026–85.97, OR= 24.77 CI 5.82–105.3, Chi-square= 35.73 with p < 0.0001)*, those who need to travel a distance of more than 30 minutes walk *(RR = 4.38 CI 2.22 – 8.63, OR = 5.12 CI 2.41 – 10.88, Chi-square= 19.37 with p<0.0001),* those who need to buy medicine occasionally *(RR= 2.3 CI 1.173–4.51, OR= 2.48 CI 1.18 – 5.23, Chi-square = 5.08 with p = 0.024)* and those subjects who were directly observed by health care provider during intensive phase *(RR – 14.483 CI 4.95–42.374, OR= 18.77 CI 5.90–59.67), Chi-square = 37.69 with p < 0.0001).*

The treatment outcome in relation to potential risk factors for non-compliance and default along with the statistical analysis are given in Table 2.

DISCUSSION

The study results are quite interesting while comparing the treatment interruption rate of 7.4% or the default rate of 5.9% with similar studies conducted during the last 8 to 10 years in the region. A study showed default rate of 8%,[15] another showed a default rate of 23%,[16] and another showed a default rate of 20%.[17] Most of the patients defaulted within first few months of treatment, as shown by this study in Ethopia,[17] while a study by Chan Yeung and fe-

llows[15] showed that 45% of defaulters did so in the first 2 months of treatment, both showed early defaulters to be more. On the other hand the study by Daniel in Nigeria[16] determined that defaulting rate was highest (78.1%) during the continuation phase of the treatment, supporting our results, which showed 18 / 31 (58%) patients got treatment interruption during continuation phase.

A number of factors were found linked to an increased chance that the person would default from treatment. These included age (patients over 25 were less likely to complete); living in a rural setting; having a lower level of education; greater distances from home to the treatment centre; the need for transport to get to treatment; and whether the patient was admitted to hospital in a serious condition.[17] Our study results showed increased probability of treatment interruption in patients with following factors; the need to travel for medicine, more than 30 minutes walking *($p < 0.0001$)* distance of treatment centre or the centre from which they get the medicine from their home, need to buy medicine *($p = 0.024$)*, direct observation by the health care provider during intensive phase *$p < 0.0001$)*.

Weak risk factors in the present study which might be associated with treatment interruption are being non-working, income less than $1 per capita per day, having apprehension and myths regarding medicines, changes done in diet due to treatment of tuberculosis (thus placing economic burden on the family) and direct observation had been made in intensive phase *(RR – 1.75)*. On the other hand, age more than 25 years and being single / unmarried were not the risk factors for treatment interruption. Patient education *(RR = 0.75)* and feeling of being stigmatised posed a reduced risk for treatment interruption *(RR = 0.92)*.

While considering association of gender with high default, it is found in studies that male sex is an important risk factor associated with non-compliance,[15-18] while our finding showed female gender is a risk factor for treatment interruption. This might be due to lack of authority for decision making and other physical, psychological, domestic and cultural issues along with illiteracy in Pakistani women.

It was concluded that the treatment default could be predicted fairly accurately by considering patient and treatment – related factors.[19] Our study showed the role of direct observation to be quite important as the results suggests that subjects being not directly observed especially during intensive phase are at risk for treatment interruption. A similar kind of study conducted in Nigeria on compliance in pulmonary tuberculosis patients using directly observed treatment short course concluded that the use of DOTS with free drug provision and the use of home visitor as used in this study confirmed its effectiveness in enhancing compliance and hence cure of Pulmonary TB.[30] Our finding showed that treatment interruption and default were more in patients being observed by a health care provider than being observed by a family member or a neighbour. Qualitative studies showed that patients who received the support and care of their families were more likely to adhere to therapy and achieve cure.[21] Furthermore, a cluster RCT in South Africa reported improvements when lady health workers were involved in TB control,[22] although a study in Nepal,[23] recently demonstrated that both family and community DOT supporters can achieve good treatment outcomes. A study on role of "TB clubs" in changing societal attitudes and behaviour associated with TB. The defaulter rate was also significantly lower *($X^2 = 11.57$, $P < 0.001$)* in the TB club (12.5%) compared to (40.6%) in the comparison group.[24] This study also supports the importance of family and community involvement in DOTS. Role of family or any community member in direct observation to improve compliance might be due to the fact that this treatment supporter belongs to the same community, with same socioeconomic and cultural background. The counselling or advice of this person will be more effective than a busy health care provider because the patient needs emotional support rather than plain advice to swallow the bulk of tablets on daily basis. This study will be of value assessing the effectiveness of DOTS strategy and also an insight into the risk factors for treatment interruption, which can be modified through organised efforts at grass root level.

It is ***concluded*** that direct observation by family members / neighbors or a responsible person in the family is of a definite value in prevention of non-compliance or default in TB high burden countries like Pakistan. Other factors need to be eliminated or modified like travelling for medicine, need to buy medicine. If these factors are addressed properly we can implement DOTS more effectively.

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