Middle-East Journal of Scientific Research 11 (7): 873-880, 2012
ISSN 1990-9233

A Comparison of Directly Observed Therapy and Self-Administered Therapy Strategies in Treatment of Pulmonary Tuberculosis: A Cohort Study in North of Iran

[1]Mahmood Moosazade, [2]Mohammad Jamshidi,
[3]Mohammadreza Amiresmaili and [4]Asghar Nezammahalleh

[1]Research Center for Modeling in Health, School of Health,
Kerman University of Medical Sciences, Kerman, Iran
[2]Ministry of Science, Research and Technology
[3]Department of Health Services, Kerman University of Medical Sciences
[4]Mazandaran University of Medical Science, Sari, Mazandaran, Iran

Abstract: Weak diagnosis, inadequate and incorrect treatment, emergence of drug resistance and HIV co-epidemic has caused serious problems for tuberculosis control program. The aim of this study was to investigate the efficiency of DOTS strategy in treatment of patients with positive smear pulmonary tuberculosis. This Cohort study was carried out on patients with positive smear pulmonary tuberculosis registered in Mazandaran Diseases Control Center (Iran) from 2005 to 2010. Of 683 registered patients, 362 were in Directly Observed Therapy group and 321 ones were in Self-Administered Therapy group. Specifications of field variables in both groups and their homogeneity were studied using analytical analysis and then treatment results were compared in both groups using Poison Regression and Chi^2 analysis; analysis of treatment results have also been presented in subgroups. 48.1% of patients were male. Patients' average age was 49.73±21.57 years and no significant difference was observed among different ages in terms of their gender (P=0.8). In directly observed therapy group, success and failure levels were 92 and 8 percent respectively, while it was 83.2 and 16.8 in self-administered therapy group. Treatment success in self-administered therapy group was 2% less than that of WHO, while in directly observed therapy group it was 7% more than that of WHO. In a case all health and treatment centers use directly observed therapy, treatment success level will exceed 90% which is beyond the objectives determined by WHO.

Key words: Tuberculosis · Treatment · DOTS

INTRODUCTION

Tuberculosis (TB) remains a global emergency with estimates of 1.8 millions deaths and over nine million infected cases in 2008 [1]. Early diagnosis of tuberculosis and effective treatment are the key elements in reduction of transmission of infection and finally achieving elimination of TB [2]. World Health Organization (WHO) has set the international target value for a treatment success outcome at 85% [3]. The WHO reports worldwide success rates for tuberculosis treatment range from 20-87% [4]. In report from Finland, a favorable outcome was reached in only 65%, death being the outcome in as much as 19% and defaulting, transferring out or physician's decision to stop treatment early were reasons of other unfavorable outcomes in 12% of the cases [5].

Uncompleted treatment course and not entirely cured cases, not only do not remove themselves from the prevalence pool but are going to add more infected cases and are associated with recurrence of TB [6]. Recurrent tuberculosis causes significant threats like MDR-TB and HIV-associated TB that can be counted as problems resulted from improper TB treatment [7].

Without sufficient adherence, not only does TB remain uncured, but also provides the opportunity to mutate into drug-resistant forms [8].

Corresponding Author: Mohammadreza Amiresmaili, Department of Health Services Administration, Kerman University of Medical Sciences, Iran.

According to previous studies, even in industrialized countries and among knowledgeable and educated individuals at least 30% of patients, owing to a perception of improvement, do not take their medication properly and stop treatment after a while [9]. To improve adherence to treatment, directly observed therapy (DOT), in which patients are observed ingesting each dose of anti-tuberculosis medications, is recommended as the standard treatment of pulmonary tuberculosis by several leading international organizations [10]. DOTS was first piloted in the 1950s to ensure adherence to and treatment completion. Because of reports on success of DOT in increasing treatment completion rates and preventing drug resistance, WHO adopted DOT as a principal component of its global TB control strategy [11].

In Directly observed treatment strategy (DOTS), in addition to direct observation of drug consumption, having a standard regimen for treatment and follow-up of patients improves the success rate. Conversely, for the reasons outlined above, treatment regimens other than DOTS have a low success rate and may lead to TB transmission in the community and mycobacterial drug resistance [9].

The strategy, although based around short course treatment regimens for a minimum of six months, also includes tenets such as political commitment, good management practices, sputum smear microscopy for diagnosis and the direct observation of doses to ensure adherence. To date DOTS remains the cornerstone of global efforts for tuberculosis control [12].

Previous studies throughout the world indicate that by using DOTS strategy, the success rate of treatment is about 90-95%, or even higher [9].

By 2005, 187 countries were implementing DOTS, with 4.9 million cases of tuberculosis treated under the strategy in that year alone [12]. WHO reports that 84% of new (previously untreated) patients registered with DOTS worldwide in 2004 were "successfully treated [13]. Abassi and Aarabi [14] in the study of efficacy of DOTS strategy in treatment of respiratory tuberculosis in Gorgan of Iran reported that in the DOTS group, 91.0% were smear negative at the end of the 2nd month and 98.3% at the beginning of the 5th month. Whereas, in the non-DOTS (control) patients without direct observation, the corresponding values were 81.7 and 92.6% ($P < 0.05$).

Concerning relative long treatment period of 6 months for tuberculosis and consumption of 4 or 5 types of drugs in a day, side effects of anti-tuberculosis drugs, patients' reluctance to take drugs for a long time, not continuing drugs after a relative recovery, we can find the importance and key role of DOTS in treatment success of this disease. However, some patients take anti-tuberculosis drugs without supervision of health personnel due to some reasons including inadequate access, lack of health personnel, patients' unwillingness to take drugs under supervision of health personnel, patients' dissatisfaction with being visited by the health personnel every day in their houses and patients and their families' inadequate information. This cohort study has been carried out (7 years after the last article) to study the efficacy of DOT strategy in north of Iran.

MATERIALS AND METHODS

Patients Diagnosis and Management: This cohort study was carried out in the province of Mazandaran with the population of 2,450,000. In this study, all 683 patients whose smear positive pulmonary tuberculosis was registered from 01/03/2004 to 20/03/2010 in Mazandaran Diseases Control Center were studied. Patients were diagnosed using Ziehl-Nielsen technique. Recommended regime for TB treatment in the study period consisted of isoniazid (INH), rifampicin, ethambutol and pyrazinamide [15]. All of the TB cases underwent a 6 or 8-month treatment regimen according to WHO protocol: 2 months with 4 drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) and 4 months with 2 drugs (isoniazid and rifampicin) for new cases and 2 months with 5 drugs (isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin) and 1 month with 4 drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) and 5 months with 3 drugs (isoniazid, rifampicin and ethambutol) for retreatment cases [15].

During the treatment period, sputum samples were taken at the end of the 2nd month and at the beginning of the 5th month. Patients who were smear-positive after the 2nd month would have an extra month on the 4-drug regimen. Those smear-positive at the beginning of the 5th month were considered treatment failures.

DOT Strategy Execution Trend and Follow Up: When a patient with tuberculosis was diagnosed, he was referred to the nearest health center to undergo DOTS; in that center, a treatment card and a patient's card were issued for him. Treatment card included patient's demographic information, disease diagnosis date, disease type, treatment regime type (category I, II) based on his previous tuberculosis record, treatment date and timetable

for registering drug consumption by the patient in invasion and prevention phases. Days in which the patient took drugs with direct supervision of health personnel were specified with ×, days in which he took drug without direct supervision were specified with - and days in which he didn't take drug had no sign. This treatment card is kept in health treatment center. Patient's ID card includes patient's specifications and his present treatment; it is kept with him. All patients and their families were trained on the importance of drug consumption, patients' unwillingness to take drug, probable side effects of the drugs, reasons of direct observation of health personnel, DOTS supervision type and how to control drug effects. All patients were followed up for 6 (treatment regime I) and 8 (treatment regime II) months based on their therapeutic regime [15]. In a case the patient took drugs under direct supervision of the health personnel, he was categorized in DOTS group, otherwise he was categorized in Non-DOTS group; then, treatment results were determined and compared in both groups. In this study, ethical considerations were fully observed as all patients and their families were trained, a DOTS executive person was determined for every patient and patients and their families were the ones who finally decided how to take drugs. Also, treatment results were reported and published without mentioning the name of the patients and with the permission of Disease Management Center of Mazandaran Health Deputy. Moreover, in addition to mentioning the name of Mazandaran University of Medical Science in acknowledgement section, tuberculosis coordinating expert who had an effective role in collecting data is one of the authors (Asghar Nezam Mahalleh).

At the end of the follow up period, 362 patients were placed in DOTS group and 321 ones in non-DOTS group. Table 1 shows specifications of the studied patients; there was no meaningful difference between both groups regarding age, gender, previous treatment record, sputum smear level at the beginning of the period and nationality.

Definitions of Treat Outcome: The treatment outcome was divided into six categories according to WHO guidelines, with some modifications [15].These categories were:

Cure Rate: A person who completed all prescribed doses, didn't have treatment failure and was documented to have two or more consecutive negative cultures within 6 months of treatment initiation.

Completion of Treatment: Completion of all prescribed doses but lacking bacteriologic proof of cure because of inability to produce sputum.

Treatment Success: The sum of cure rate and completion of treatment.

Died: A patient who died during the treatment course irrespective of the cause.

Transferred Out: A patient who was transferred to another treatment center and for whom treatment results were not known.

Treatment Failure: A smear-positive patient who remained smear-positive at the fifth month of treatment.

Defaulted: A patient who did not come back to complete chemotherapy and there was no evidence of cure through the sputum result during the fifth month of therapy.

Unsuccessful Treatment: The sum of died, treatment failure, defaulted and transferred out.

The outcome was categorized as favorable (Treatment success) that was defined as the sum of the cases that were cured and completed treatment and as unfavorable (unsuccessful outcome or failure, death, default and transfer out) [15].

Data Analysis: ield variable specifications of both groups and their homogeneity were studied using analytical analysis; Chi square or Fisher's exact test (in a case the expecting number in every cell was less than 5) was used for categorized variables. Average age of both groups was compared using independent T-Test. Treatment results in both groups were compared using Poison and regression analysis. Treatment results analysis was also presented for subgroups. Relative risk, confidence interval and significance level were calculated among treatment results (treatment success versus nonsuccess) regarding DOTS method. P-values less than 0.05 were considered significant. Statistical analysis was done using Stata 11 Software.

RESULTS

Average prevalence of all tuberculosis and smear positive pulmonary tuberculosis from 2004 to 2009 was 9.1 and 4.3 per one hundred thousand people respectively.

Table 1: Distribution of patient characteristics in the two groups

Parameter value		Directly observed Therapy	Self-administered therapy	X2 or T-test	p
No. (%)		362(53)	321(47)	-	-
Age	Mean (SD)	48.97±20.7	50.5+22.5	0/9-	0.4
Age group	< 65 years (%)	55.8	44.2	4.8	0.03
	≥ 65 years (%)	46.6	53.4		
Gender	Male (%)	52.4	47.6	0.1	0.4
	Female (%)	53.8	46.2		
Positive smear Grade in the first treatment	≤ 2+ (%)	52.3	47.7	0.4	0.5
	≥ 3+ (%)	54.9	45.1		
Last cure	No (%)	52.8	47.2	0.1	0.4
	Yes (%)	55.3	44.7		
Nationality	Iranian (%)	53.8	46.2	4	0.06
	Non Iranian (%)	35.5	64.5		
Resident area	Urban (%)	48.2	51.5	8.5	0.004
	Rural (%)	59.5	40.5		

Table 2: Comparative treatment and sputum smear results in the two groups

Variable		Directly observed Therapy (n)%	Self -Administered therapy (n)%	p-Value
Treatment Result(1)	Successful	(333)92	(267)83.2	0.0001
	Defaulted	(3)0.8	(15)4.7	
	Failure	(0)0	(14)4.4	
	Died	(13)3.6	(17)5.3	
	Transferred	(13)3.6	(8)2.5	
	Total	(362)100	(321)100	
Treatment Result(2)	successful	(333)92	(267)83.2	0.01
	Non-Successful	(29)8.01	(54)16.8	

Table 3: Comparative treatment results of variables and patient characteristics in the two groups

		Directly observed therapy			Self-administered therapy		
Parameter		Successful outcome (%)	Non successful outcome (%)	p-value	Successful outcome (%)	Non successful outcome (%)	p-value
Gender	Male	88.8	11.2	0.01	81.3	18.7	0.3
	Female	96.2	3.8		85.8	14.2	
Nationality	Iranian	93.2	6.8	0.001	84.1	15.9	0.1
	Non Iranian	54.5	45.5		70.0	30.0	
Resident area	Urban	91.0	9.0	0.5	83.7	16.3	0.7
	Rural	93.1	6.9		82.2	17.8	
History of last cure	No	92.6	7.4	0.1	83.3	16.7	0.8
	yes	84.6	15.4		81.0	19.0	
Sputum smear result at the end of	Negative	99.3	0.7	0.0001	96.8	3.2	0.0001
second month	Positive	52.6	47.4		37.8	62.2	
Age group	<65years	92.5	7.5	0.7	83.9	16.1	0.6
	>65years	90.6	9.4		81.8	18.2	
Positive smear grade in the first treatment	≤2+	93.3	6.7	0.2	86.3	13.7	0.02
	≥3+	88.8	11.2		75.0	25.0	

683 patients with smear positive pulmonary tuberculosis were recognized from 2004 to 2009; of them, 48.1% were male and 51.9% were female (P≥0.05, OR=0.87, 95%CI=0.79-0.95). Their average age was 49.73±21.57 (males and females' average age was 49.8±20.8 and 49.4±22.6 respectively). No significant difference was observed regarding their age and gender (P≥0.05).

362 (53%) of them were placed in DOTS group and 321 (47%) were placed in Non-DOTS group; observed differences in both groups were not significant regarding age, gender, previous treatment record, nationality and sputum smear level. In other words, both groups were similar in terms of field variables and demographic characteristics (P>0.05). However, their differences were significant concerning age group residing area (P=0.004); to remove the bad effects, treatment results were also presented for subgroups (Table 1).

Treatment results for all patients with smear positive pulmonary tuberculosis showed that 87.8% of cases had successful treatment; 2.6% of patients were defaulted; in 2%, treatment was failed; 4.4% of cases died; and 3.1% were transferred cases. In DOTS group, treatment success was 92%; patients' absence was 0.8%; treatment failure was 0%; death was 3.6%; and 3.6% were transferred cases. In Non-DOTS group, treatment success was 83.2%; 4.7% were defaulted; treatment failure was 4.4%; death was 5.3%; and 2.5% were transferred cases. Differences observed in results of both groups were significant statistically (P= 0.0001) (Table 2).

In univariate analysis, differences observed in results of DOTS group were meaningful in terms of gender, nationality and results of sputum smear at the end of the second month of treatment (P<0.05) (Table 3).

Also, in univariate analysis, differences observed in results of Non- DOTS group were meaningful in terms of results of sputum smear at the beginning of treatment and at the end of the second month of treatment (P<0.05) (Table 3).

DISCUSSION

Based on the findings of the present study, level of treatment success in all patients with smear positive pulmonary tuberculosis was 87.8% and its non-success rate was 12.8%. In DOTS group, the success and non-success rates were 92 and 8% respectively, while in Self-Administered Therapy group they were 83.2 and 16.8% respectively. In other words, success rate in DOT group was 1.1 times more than that of Self-Administered group; that is, treatment success in DOT group is 10% more than that of Self-Administered group (P=0.2, RR=1.1,95%CI=0.9-1.3). Failure level and patients' absentee in Self-Administered group were higher than that of DOT group (4.4%vs. 0% and 4.7% vs. 0.8% respectively). Also, treatment success index in terms of all field and demographic variables (except for nationality for which non Iranian patients had lower treatment success in DOT group compared to Iranian patients) in DOT Group was higher than Self-Administered group.

In a study carried out in Golestan Province, treatment failure in DOTS group was 1.7%, while it was 7.3% in Non-DOTS [6]. Siadati *et al.* [16] reported that failure rate in the case group is 1.5 times less than that of control group. In a research, in which 149 tubercular people in DOTS group and 223 ones in Non-DOT group took drugs, the result was more desirable for DOT group than Non-DOTS group and a significant relationship was observed statistically (P<0.002) [17]. Also, a study carried out in Baltimore, America revealed different responses to treatment in both groups; treatment failure in DOTS group was 4 %, while it was 38% in the other group [18]. A five-year study carried out in India on DOT patients showed that treatment failure was 6.1% [19]. Also, according to WHO report and based on a study carried out in Iraq, it was shown that treatment success in DOT group was 96.2%, while it was 76.2% in control group and treatment failure in DOT was 0.9%, while it was 10% in control group [20] that it highlights the importance of DOTS strategy. In all studies mentioned above, treatment success in DOT group was higher than non-Dot group and treatment failure was less and it matches the present study. However, treatment failure in both groups' case and control was higher than the present study.

In a study carried out by Jasmer *et al.* [21], treatment success in DOTS group was significantly higher than that of Self-Administered therapy (97.8% vs. 88.6%, P<0.0002); it shows high efficiency of DOTS strategy.

In another study in Turkey [22], it was emphasized that DOTS strategy increased success rate in all patients especially those with risk factors that lessened their treatment success.

Directly observed therapy (DOT) is advocated by WHO and the International campaign against tuberculosis and lung disease as one solution to the problem of adherence and emerging drug resistance [23].

Thus, consumption of anti-tuberculosis drugs correctly and regularly under direct supervision of reliable people can reduce failure and disease spread.

Studies carried out in different parts of the world revealed that DOTS can increase treatment success to 90-95% and even more. In DOTS, in addition to taking drugs under direct supervision of health personnel, a standard method is used to treat and observe disease, side effects and unsuitable responses are determined

quickly and suitable decisions are made to continue treatment trend which can maximize treatment success; without DOTS, on the other hand, treatment success decreases to 85% which results in disease spread in the society and increased cases of treatment resistant tuberculosis [24-27].

One of the problems we face in treating patients with tuberculosis is that patients have to take different types of drugs every day (at least 4 to 5 types of medicines every day) and that they can't bear this situation so they cut it without informing the health and treatment system.

Many authors have proposed methods of improving the control of drug intake, such as blood or urine tests to check the presence of the TB drugs and electronic devices to monitor time of drug intake and improve adherence to TB treatment by educating the patients and their families, incentives (bus fares, meals etc), letters or phone calls to recall appointments. Fixed drug combinations have also been advocated as a means of making treatment less complex [28].

In this study, 47% of patients with smear positive pulmonary tuberculosis were voluntarily placed in self-administered therapy and weren't willing to use DOTS; the reasons can be cultural obstacles, disease disreputability, bad behavior of health and treatment personnel and lack of confidentiality which have all been confirmed by Bagchi *et al*. [29].

In a univariate and multivariate analysis, Mishra *et al*. [30] found a statistically significant relationship between weak communication of health personnel and supervisors with patients and patients' unwillingness to take drugs.

The ultimate ethical and legal responsibility for ensuring treatment completion and cure of a communicable disease belongs to the public health system and the community and not to the individual patient. TB can be controlled when appropriate policies are implemented and continued, even in the absence of an outbreak or media attention. Just as patients may be tempted to change or stop an effective treatment regimen because of the long duration of treatment, public health policy-makers may be tempted to alter key elements of DOTS because of the persistence required to maintain effective programs [31].

According to the World Health Organization a TB program should attain a success rate of more than 85% [11]. The rate of unfavorable outcomes should be under 10% after exclusion of death cases [32].

CONCLUSIONS

In the present research, treatment success in all patients with smear positive pulmonary tuberculosis was more than the targets set by the WHO; which highlights the efficiency of DOTS strategy on patients with tuberculosis. Treatment success in self-administered therapy group was 2% less than the objectives of WHO, while in DOT group it was 7% higher. If health and treatment centers apply DOTS method for all tubercular patients, treatment success will increase to 90% (that is more than the objectives determined by WHO). In this case, risk of spreading tuberculosis resistant to treatment (MDR and TDR) will decrease and achieving millennium development objectives will become easier.

ACKNOWLEDGEMENTS

The authors wish to thank respected Health Deputy, Diseases Group Manager, Health Deputy, Tuberculosis Cooperating Expert and Tuberculosis Cooperating Physicians in Health and Treatment Networks of cities covered by Mazandaran University of Medical Science for their sincere cooperation in collecting necessary data and information.

REFERENCES

1. WHO (World Health Organization), 2009. Global tuberculosis control: a short update to the 2009 report. Geneva: World Health Organization;. Available from: http:// www.who.int/ tb/ publications/global_report/2009/update/tbu_9.pdf.
2. WHO (World Health Organization), 2006. The Stop TB Strategy: Building on and Enhancing DOTS to Meet the TB-related Millennium Development Goals, Geneva: WHO; 2006. Available from: www.who.int/stb//htm.
3. WHO (World Health Organization), 2007, Global tuberculosis control, WHO Report; 2007. Available from: www.who.int.
4. WHO (World Health Organization), 2009. Global tuberculosis control. Epidemiology, strategy, financing, WHO report 2009.Available at: http://www.Who.int/tb/publications/global_report/ 2009.
5. Vasankari, T., M. Kokki, P. Holmstrm, K. Liippo, S. Sarna and P. Ruutu, 2007. Great diversity of tuberculosis treatment in Finland. Euro Surveill., 12(1): [Epub ahead of print]: PMID: 17370977.

6. Picon, P.D., S.L. Bassanesi, M.L.A. Caramori, R.L.T. Ferreira, C.A. Jarczewski and P.R.B. Vieira, 2007. Risk factors for recurrence of tuberculosis. Journal Brasileiro De Neumologia, 33: 572-578.
7. Juzar, A., 2005. The Many Faces of Tuberculosis Control and the Challenges Faced, Business Briefing: US Respiratory Care, 1: 1-4.
8. WHO, 2006. Global tuberculosis control: surveillance, planning, financing WHO report 2006. Geneva: World Health Organization, Available from:http://www.who.int/tb/ publications/ global_report/en/.
9. WHO, 2001. Global tuberculosis control. WHO Report 2001. Geneva, World Health Organization. Available from:http: //WHO/CDC/TB/2001.287.
10. Enarson, D.A., H.L. Rieder, T. Arnadottir and A. Trebucq, 2000. Management of tuberculosis: a guide for low income countries, Paris: International Union against Tuberculosis and Lung Disease, 5th ed.
11. Dye, C., C.J. Watt, D.M. Bleed, S.M. Hosseini and M.C. Raviglione, 2005. Evolution of tuberculosis control and prospects for reducing tuberculosis incidence, prevalence and deaths globally. J. Am. Med. Assoc., 293: 2767-2775.
12. WHO, 2006. The stop TB strategy, Building on and enhancing DOTS to meet the TB-elated millennium development goals. Geneva: Report WHO, Available from:http: // WHO/HTM/STB/2006.37.
13. WHO, International Union Against Tuberculosis and Lung Disease, Royal Netherlands Tuberculosis Association. Revised international definitions in tuberculosis control." Int. J. Tuberc. Lung. Dis., 5(3): 213-5.
14. Abassi, A. and M. Aarabi, 2004.The efficacy of DOTS strategy in treatment or failure of treatment in respiratory Tuberculosis Journal of Gorgan University of Medical Sci., 6(1): 78-82. (Persian).
15. Nasehi, M. and L. Mirhaghghani, 2010. Guidelines for combat with TB, Disease Management Center of Health Ministry, Arjemand Publication, pp: 6-44. (Persian).
16. Siyadati, A., A. Lameei and T. Afshani, 2003. Examinethe feasibility of direct supervision to the treatment of tuberculosis in the city of Urmiain three years 1998-2001, the J. Urmia University of Medical Sci., 14(1): 27-31. (Persian).
17. Robert, M., B. Christopher, C. Seaman, L. Gonzalez, H. Dennis and L. Osmond, 2004. Tuberculosis Treatment Outcomes, American J. Respiratory and Critical Care Medicine, 170: 561-566.
18. Arora, V.K., N. Singla and R. Sarin, 2003. Profile of geriatric patients under DOTS in Revised National Tuberculosis control Programme. Indian J. Chest Dis. Allied Sci., 45(4): 231-5.
19. Sudeep, N., L. Anuradha, O. Olugbenga and E. Richard, 2000. Errors in the treatment of tuberculosis in Baltimore. American College of Chest Physicains. Chest., 177: 734-737.
20. Mohan, A., H. Nassir and A. Niasi, 2003. Does routine home visiting improve the return rate and outcome of DOTS patients who delay treatment? Operational. Research in Tropical Diseases. East Med. Health, 9(4): 702-8.
21. Jasmer, R.M., C.B. Seaman, L.C. Gonzalez, L.M. Kawamura and C.L. Daley, 2004. Tuberculosis Treatment Outcomes: Directly Observed Therapy Compared with Self-Administered Therapy, Am. J. Respir Crit Care Med., 170: 561-566.
22. Talay, F., S. Kumbetli and S. Altin, 2008. Factors associated with treatment success for tuberculosis patients: a single center's experience in Turkey. Jpn. J. Infect Dis., 61(1): 25-30.
23. Gupta, S., D. Berg, F. De Lott, P. Kellner and Driver, 2004. CDirectly observed therapy for tuberculosis in New York City: Factors associated with refusal. International J. Tuberculosis and Lung Dis., 8: 480-485.
24. Frieden, T.R. and J.A. Sbarbaro, 2007. Promoting adherence to treatment for tuberculosis: the importance of direct observation. Bulletin of the World Health Organization, 85(5): 407-9.
25. Lucas, G.M., C.W. Flexner and R.D. Moore, 2002. Directly administered antiretroviral therapy in the treatment of HIV infection: Benefit or burden? AIDS Patient Care and STDs., 16(11): 527-35.
26. Tulsky, J.P., J.A. Hahn, H.L. Long, D.B. Chambers, M.J. Robertson, M.A. Chesney, *et al.*, 2004. Can the poor adhere? Incentives for adherence to TB prevention in homeless adults.The International J. Tuberculosis and Lung Dis., 8(1): 83-91.
27. Walley, J.D., M.A. Khan, J.N. Newell and M.H. Khan, 2001. Effectiveness of the direct observation component of DOTS for tuberculosis: a randomized controlled trial in Pakistan. Lancet, 357: 664-669.
28. Moulding, T., A.K. Dutt and L.B. Reichman, 1995. Fixed-dose combinations of antituberculous medications to prevent drug resistance. Ann. Intern Med., 122: 951-4.

29. Bagchi, S., G. Ambe and N. Sathiakumar, 2010. Determinants of Poor Adherence to Anti-Tuberculosis Treatment in Mumbai, India, IJPM, 4(1): 223-232.
30. Mishra, P., E.H. Hansen, S. Sabroe and K.K. Kafle, 2006. Adherence is associated with the quality of professional-patient interaction in Directly Observed Treatment Short-course, DOTS, Patient Education and Counseling, 63(1): 29-37.
31. Frieden, T.R. and J.A. Sbarbaro, 2007. Promoting adherence to treatment for tuberculosis: the importance of direct observation, Bulletin of the World Health Organization, 85(5): 407-409.
32. Broekmans, J.F., G.B. Migliori, H.L. Rieder, J. Lees, P. Ruutu, R. Loddenkemper, *et al*., 2002. European framework for tuberculosis control and elimination in countries with a low incidence. Eur. Respir J., 19: 765-75.