Factors Influencing Sputum Smear Conversion at One and Two Months of Tuberculosis Treatment

Sumant Pajankar,[1] Rajiv Khandekar,[2] Musallam Amer Al Amri,[1] Mohammed Redha Al Lawati[1]

Abstract

Background: In the era of Direct Observation Treatment (DOT) for tuberculosis, clinicians need to focus on high-risk groups. We present sputum conversion rate at one and two months following DOT and its predictors in Oman.

Study design: Hospital-based clinical intervention type of case series.

Methods: Chest physicians in a referral hospital examined sputum-positive cases of tuberculosis between 2001 and 2006. Patients with HIV infection and treated in the past were excluded. History of smoking, diabetes and duration of symptoms were noted. Sputum was tested for bacillus density. Blood was tested for platelet count and blood sugar levels. One and two months following treatment, the sputum was retested to determine sputum conversion. Regression analysis was done to identify the predictor of late conversion.

Results: Of the 112 sputum-positive TB cases, 39 (34.8%) and 49 (43.7%) cases were sputum negative one and two months respectively after DOT. Lower platelet count was significantly associated with early sputum conversion. (Diff of mean = 38.3 cells x 9/L (95% CI 36.9 – 39.7). On univariate analysis, duration of symptoms, history of diabetes, smoking and ESR were not associated with the early sputum conversion. Knowledge of platelet count seems to assist the clinician to predict the early sputum conversion following DOT for pulmonary TB.

Conclusions: Sputum conversion rate among tuberculosis patients treated with DOT for one and two months in Oman was 34.8% and 78.6% respectively. Platelet count could assist in predicting early sputum conversion.

Keywords: Tuberculosis; Direct Observation Treatment (DOT).

Received: 07 Aug 2008
Accepted: 10 Sept 2008

From the [1]Department of Medicine, Al Rahma Hospital, Ministry of Health, Muscat, Oman; [2]Eye & Ear Health Care, Department of Non-communicable Diseases Control, Directorate General of Health Affairs, Ministry of Health, Oman.
Address correspondence and reprint request to: Dr. Rajiv Khandekar, Eye & Ear Health Care, NCD, DGHA, MOH (HQ), P.O. Box 393, Pin 113, Muscat, Oman. Email: rajshpp@omantel.net.om

Introduction

Sputum Acid Fast Bacilli (AFB) positive Pulmonary Tuberculosis is the infectious form of tuberculosis and is mainly responsible for transmitting the disease. An untreated patient is likely to infect another 10-15 cases each year. Transmission is through droplet nuclei, which are airborne from the index cases.[1] Susceptibility of developing tubercular infection depends upon bacillary load, close contact with the patient and duration of antitubercular treatment.[2]

On starting effective antitubercular treatment, bacillary load decreases rapidly, which correlates with reduced infectivity.[3] In spite of various serological markers, sputum AFB remains the important measure for the treatment response.[4] Delay in sputum, AFB smear conversion at 2-3 months is one of the predictors of treatment failure and relapse.[5, 6]

Al Rahma, where the present study was undertaken, is a referral hospital to manage patients with tuberculosis in Oman. Physicians refer all cases of tuberculosis both from Ministry of Health institutions and the private sector to this hospital for special care. Sputum AFB (Acid Fast Bacilli) smear-positive cases from Muscat region only are admitted in this hospital.

We conducted this study to estimate sputum AFB smear conversion rate at one and two months, and associate selected risk factors to the delay in sputum AFB smear conversion. Based on the study outcome, we proposed policies for treating tuberculosis in Oman.

Methods

We obtained approval of the hospital ethical committee to undertake this study. This was a hospital-based descriptive study. We conducted this study to review cases treated between January 2000 and December 2005.

Although few cases of tuberculosis are reported through active surveillance in Oman, it will be interesting to study risk factors of poor response of conventional antitubercular treatment among the Omani population.[7] Hence, we conducted this study in a hospital of Oman. We assumed that in our study population, delayed sputum conversion will be in 75% of cases. [8] To achieve 95% confidence interval and 90% power of the study in a group of sputum converted and sputum not converted at the end of two months with a ratio of 1:2, we needed 34 persons with nonconversion at the end of one month and 68 persons in sputum conversion group at the end of two months. Thus, to test the hypothesis, the minimum sample required in our study was 112 persons with pulmonary tuberculosis.

Two physicians and an epidemiologist were the study investigators. All patients with pulmonary tuberculosis from different hospitals and health centers of the Muscat region, Oman, that were referred from 2000 to 2005 were included in our study. These patients were newly diagnosed with sputum positive for AFB and Mycobacterium sensitive to the first line of anti-TB treatment. Drug-resistant relapse cases and patients with HIV infection were not included in our study.

As per the policy of the Ministry of Health, all sputum AFB-positive Pulmonary Tuberculosis cases are admitted in our hospital to ensure supervised treatment of two months duration. At the time of admission, blood was collected for tests such as complete blood count (CBC), erythrocyte sedimentation rate (ESR), blood sugar, HIV, liver function test (LFT), and renal function test (RFT).

Sputum was collected for testing culture for AFB and its sensitivity to conventional antitubercular antibiotics. For AFB culture, we used Lowenstein-Jensen solid medium and BACTEC (Becton Dickenson) liquid medium. Laboratory technicians were trained in the field of tuberculosis stained and reported sputum AFB smear slides. Routinely, some of these slides selected randomly were sent to Central Laboratory for quality control. Sputum was stained with Ziehl-Neelsen technique. Positive slides for AFB were categorized into (1) 1 to 9 / 100 fields, (2) 10 to 99/100 fields, (3) 100 to 999/100 fields and were labeled as +, ++, +++ respectively.

Chest physicians determined cavitations, laterality of lung involved and presence of consolidation or other complications such as effusion and hilar lymph node involvement. In few cases, opinion of radiologist was obtained on x-ray chest.

Each patient's demographic profile, clinical details (symptoms, physical findings), results of radio imaging, sputum status, blood investigations, diabetes mellitus/smoking history, treatment details, and treatment outcomes were recorded.

The disease classification, treatment protocol, and evaluation of treatment outcome of pulmonary tuberculosis were defined as per the standard guidelines.[9] The first line antitubercular treatment was started using isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E). Patients received supervised treatment for the first two months.

Sputum smears were examined for AFB every week. If sputum was found to be negative, it was repeated. Blood tests and x-ray chest were repeated after four and eight weeks of treatment. Patients were discharged at the end of eight weeks of intensive therapy only if three consecutive sputum smears were negative for AFB. Sputum AFB culture/sensitivity test was repeated at the end of two months if sputum remained positive for AFB. This was to determine whether the organisms had developed resistance to any drug. The same four antitubercular drugs were included in the regimen and continued for one more month.

The computerized case records of patients were maintained by using Al Shifa, a locally made software by the Ministry of Health. The names of the patients were de-linked and a unique identification code was given to each record. Microsoft XL ® spreadsheet was used to collect pre-tested variables from case records. The data was analyzed using univariate parametric method with help of Statistical Package for Social Studies (SPSS 11). We calculated frequencies and percentage proportion. To compare outcomes at end of one and two months, we used Risk Ratio and its 95% Confidence Interval. We also used STATCALC of EPI6 software to estimate chi-square and p values. To identify the predictors of sputum conversion at the end of two months, we conducted logistic regression analysis. Those variables having significant association in univariate analysis, age, sex, and few known variables, found to be clinically significant in other studies were entered using step-in method in the regression model.

Results

In our series, 112 persons (51 males and 61 females) were reviewed for sputum conversion at one and two months following treatment for pulmonary tuberculosis. The characteristics of the patients are given in Table 1. Twenty-eight patients were of under 20 years of age.

Table 1: Characteristics of patients with pulmonary tuberculosis (Oman TB study 2007)

		Number	Percent
Sex	Male	51	45.5
	Female	61	54.5
Age group	<20 years	28	25.0
	21 to 40	42	37.5
	41 to 60	34	30.4
	61 and more	8	7.1
Resident of (Wilayat)	Muscat	9	8.0
	Muttrah	35	31.3
	Bausher	9	8.0
	Seeb	33	29.5
	Al Amerat	12	10.7
	Quriyat	14	12.5
History of smoking	Yes	30	26.8
	No	74	67.0
	Missing	8	7.2
History of diabetes	Yes	28	25.0
	No	84	75.0
Total		**112**	**100.0**

The rate of sputum conversion at the end of one month of treatment was 34.8% while it was 44.7% between one and two months. The conversion rates for different variants were calculated. The rates at one and two months after treatment were analyzed using univariate method. (Table 2)

Table 2: Sputum conversions after one and two months of DOT for pulmonary tuberculosis and their associated factors (Oman TB study 2007)

N = 112	At end of one month (n= 39)		At end of two months (n= 49)		Validation
	Number	Percent	Number	Percent	
Total	39	34.8	49	43.7	
Sex					
Male	21	53.8	23	46.9	RR = 1.17
Female	18	46.2	26	53.1	95 % CI (0.73 – 1.87)
Age group					
<20 years	13	46.4	11	22.4	
21 to 40	15	35.7	20	40.8	$\chi^2 = 1.354$
41 to 60	8	23.5	14	28.6	df = 3
61 and +	3	37.5	4	8.2	P =0.67
Wilayat					
Muscat	4	8.0	3	8.0	
Muttrah	15	31.3	16	31.3	
Bausher	4	8.0	4	8.0	$\chi^2 = 4.11$
Seeb	10	29.5	12	29.5	df = 5
Amerat	1	10.7	7	10.7	P = 0.53
Quriyat	5	12.5	7	12.5	
History of smoking					
Yes	9	23.1	11	22.4	RR = 1.02
No	30	76.9	38	77.6	95% CI (0.59 – 1.77)
Diabetes					
No	32	82.1	36	73.5	
Yes but controlled	1	2.6	1	2.0	RR = 1.12
Yes but uncontrolled Diabetes	6	15.4	12	24.5	95% CI (0.89 – 1.40)
Lung involvement					
Unilateral	20	51.3	23	46.9	RR = 1.10
Bilateral	19	48.7	26	53.1	95% CI (0.69 – 1.76)
Cavity in lung					
Present	13	33.3	30	61.2	RR = 0.52
Absent	26	66.7	19	38.8	95% CI (0.31 – 0.88)
Duration of symptoms					
<1 month	22	56.4	16	32.7	
1 to 2	10	25.6	21	42.9	$\chi^2 = 5.45$
2 to 3	5	12.8	7	14.3	df = 4
4 to 5	1	2.6	2	4.1	P =0.24
5 + months	1	2.6	3	6.1	
Bacilli Load					
One plus	16	41.0	4	8.2	$\chi^2 = 19.1$
Two plus	10	25.6	7	14.3	df = 2
Three plus	13	33.3	38	77.6	P =0.00007
ESR					
<50 mm /1hr	10	25.6	8	16.3	RR = 1.54
≥ 50 mm /1hr	29	48.7	40	40.8	95% CI (0.67 – 3.52)

ESR: Erythrocyte sedimentation rate

At the end of one month, the platelet count in 39 patients was 408.10 cells x 10^9/L (SD 126.425), while it was 446.4 cells x 10^9/L (SD = 145.6) at the end of three months. Thus, platelet count was significantly higher at three months compared to one month (Difference of Mean = 38.3, 95% confidence interval 36.9 – 39.7). The mean level of blood sugar was 6.485 mmol/L (SD = 2.949) at the end of one month of treatment, while it was 8.34 mmol/L (SD = 5.97) at the end of three months of treatment. Thus, blood sugar level was significantly higher at the end of three months compared to the end of one month of treatment (Difference of Mean = 1.85, 95% CI 1.7 -2.0). Bacillus load, platelet count, and blood sugar levels were found to be individually and significantly associated with the sputum conversion rate.

We included age of patient and platelet count at the start of treatment as continuous variables while sex, area of residence, smoking habit, diabetes, basilar density in the sputum, ESR and the duration of symptoms in months as categorical variables in the binominal regression model. (Table 3)

Table 3. Predictors of sputum conversion at two months following DOT for pulmonary tuberculosis (Oman TB study 2007)

Predictor		Sputum conversion at 1 month				Sputum conversion between 1 and 2 months			
		Adj Odd's ratio	95% Confidence Interval		P value	Adj Odd's ratio	95% Confidence Interval		P value
Constant		8.57				-1.699			
Sex	Male	1.12	0.33	3.77	0.85	1.04	0.24	4.62	0.96
	Female	1.00				1.0			
Age		0.98	0.93	1.03	0.41	1.01	0.96	1.06	0.84
Duration of symptom	<1 month	3.17	0.29	35.09	0.35	0.31	0.03	2.86	
	1 to 2	4.64	0.48	44.89	0.19	0.20	0.03	1.66	
	2 to 3	0.56	0.04	7.05	0.65	3.71	0.35	38.92	
	4 to 5	0.37	0.02	7.29	0.51	1.74	0.13	23.74	
	5 + months	1.0				1.00			
Bacillus density	One plus	690,000	0.60	107.13	0.07	0	0.01	4.39	0.34
	Two plus	2.9				0.24			
	Three plus	1.0				1.00			
Platelet Count		1.0	0.99	1.02	0.04	1.00	1	1.009	0.07
Cavity in lung	Yes	1	0.47 – 2.52		0.84	1	0.000 – 3.61 X10^{68}		0.92
	No	1.09				0.0001			

Adj : Adjustment

The platelet count after treatment and bacilli load before treatment were the predictors of sputum conversion rates at one and two months after treatment.

Discussion

In our study, new cases of pulmonary tuberculosis two months after DOT showed sputum conversion rate of 78.5%. This rate was significantly higher compared to 34.8% at the end of the first month of treatment. Although low platelet count, area of residence and uncontrolled blood sugar were associated with the poor sputum conversion rate, we did not find any predictor that was significantly associated with the sputum conversion after two months of DOT in Oman.

There were some limitations in our study. Compared to other studies, the duration of treatment in our study was to some extent shorter. We also excluded cases of pulmonary tuberculosis with HIV and those treated for pulmonary tuberculosis in the past. Hence our study results should be compared with the outcomes of other studies with caution. The information on smoking lacked further details such as frequency, duration, type, and continuity of smoking. Perhaps, that is the reason why we could not accurately associate smoking to the sputum conversion.

We used sputum conversion as the indicator for assessing response to DOT for cases of pulmonary tuberculosis. AFB (acid-fast bacilli) in sputum smear is the diagnostic test with 95.6% specificity.[10, 11] Therefore, sputum AFB conversion is the most suitable indicator to evaluate the treatment response.[12] Hobby et. al. found that the smear and culture of tuberculosis organisms are

significantly associated.[13] But the latter test takes a longer time and often the organisms do not grow in cultures from a small sample. Hence, it is not suitable to follow up all cases being treated.

In spite of intensive treatment for two months, some patients remained sputum AFB positive. These persistently positive cases have been noted in the literature and they are due to treatment failure/relapse.[14, 15] One could argue that resistance to conventional drug therapy in patients could be the reason for non-conversion after two months in our study. The alternative explanation of non-response could be differential compliance among patients. Since all our patients were treated under direct observation, noncompliance of the medication was less likely to be responsible for resistance.

Sputum conversion rate of 78.5% at the end of two months of DOT for pulmonary tuberculosis matched with 82.4% cure rate noted by Gopi et al. and 75% by Reider HL.[16, 17] But it was still lower than 85% found in Bangladesh and 91% reported in India following a short course of DOT.[18, 19] Conversion at the end of one month of treatment in our study was only 34%. Clinicians treating cases of pulmonary tuberculosis should wait and should continue DOT as these cases at the end of two months showed better smear conversion rates. Patients with sputum positive at the end of two months constituted 21.4% of the total participants and they continued similar treatment even after two months. Further followup could show if they have additional sputum conversion at a later date. Scientists have followed cases up to two years after completion of treatment to review relapse.[20]

Gender was not associated with the sputum conversion rate in our study. Balasubramanian et al. found that males were more likely to default in taking regular medications for tuberculosis compared to female patients in India. Therefore, smear conversion rate is likely to be better in females than in males.[21] Lack of supervised treatment in developing countries, but admitting all cases of tuberculosis and providing them free of cost treatment and care in Oman could be responsible for the reduced gap among males and female patients in our study.

Patients with pulmonary tuberculosis of age <30 years responded earlier than those with more than 30 years of age. However, sputum conversion rate at two months was not significantly associated with age. Arora et al. in India observed that geriatric patients had lower smear conversion rate compared with younger patients.[22] As half the participants in our study were under 40 years of age, the effect of confounders such as diabetes and supervised treatment in elderly population ensuring adequate compliance could have resulted in insignificant association of age and smear conversion rate.[23]

Although patients with low bacillary density had a higher smear conversion rate at the end of two months in our study, the element of chance in this observation could not be ruled out. Low pretreatment bacillary load was the predictor of high cure rate in other studies.[6, 8]

Increased platelet count was a factor associated with late response to the treatment in Turkey.[24] In our study, also the low platelet count was significantly associated with early sputum conversion.

Diabetes is of epidemic proportion in >20 years old population in Oman.[25] Hence, it is essential that the role of diabetes in sputum conversion be studied. A study in India suggested that although patients with combined pathologies of pulmonary tuberculosis and diabetes mellitus had higher sputum conversion rate compared to the rate in non-diabetic patients in our study we did not find any significant association of these two factors.[26] Supervised control of diabetes for two months in hospitalized patients might have reduced the difference between non-diabetics and well-controlled diabetic patients in our study.

Hematological parameters are indirect indicators to determine the severity and type of tuberculosis.[27] High platelet count is linked to severe pulmonary tuberculosis. In our study, sputum conversion is associated with the pretreatment platelet count. Dominguez et al. indicated that high ESR seems to be associated with a longer time to convert sputum in active pulmonary tuberculosis.[28] In our study, such association was not observed.

Singla et al. found that the presence of lung cavities in a patient with pulmonary tuberculosis was associated with the delayed sputum rate following DOT.[6] Although half of the patients had cavities in their lungs, the association of cavitations and sputum conversion rate at two months was not statistically significant. Immunocompromised patients especially with HIV rate of cavitations is low.[29] As in our study we had excluded patients with HIV, such observation is logical.

We evaluated the sputum conversion based on the smear examination alone and could not confirm through testing of sputum for tubercular bacilli culture after one and two months of treatment. It is possible that smear exhibited dead bacilli but the patient responded to the DOT treatment. Perhaps culture would have shown a higher rate of sputum conversion. Different studies conducted by Singla R. et al., Gopi P G et al., A. Dominguez-Costellano et. al. studied sputum conversion rate based on the smear examination.[6,16,28] All these studies were carried out in the present decade. We recommend that studies to review the impact of tuberculosis treatment should include culture tests in the future.

We evaluated various factors associated with sputum conversion rate following two months of DOT in the Omani population. Pretreatment bacillary load and thrombocytosis were

associated with delayed sputum conversion. Variation of incidence of pulmonary tuberculosis and differential sputum conversion in wilayats of Muscat needs further confirmation. Association of factors could be better understood through a longitudinal study with a larger sample. In spite of various serological markers, sputum AFB smear remains the ideal method of diagnosing and monitoring treatment response. Delayed sputum conversion is still an area of concern due to the possibility of relapse/failure and resistance.

References

1. Telzak EE, Fazal BA, Turett GS, Justman JE, Blum S. Factors influencing time to sputum conversion among patients with smear-positive pulmonary tuberculosis. Clin Infect Dis 1998 Mar;26(3):775-776.
2. Gunnels JJ, Bates JH, Swindoll H. Infectivity of sputum-positive tuberculous patients on chemotherapy. Am Rev Respir Dis 1974 Mar;109(3):323-330.
3. Mitchison DA. Clinical development of anti-tuberculosis drugs. J Antimicrob Chemother 2006 Sep;58(3):494-495.
4. Epstein MD, Schluger NW, Davidow AL, Bonk S, Rom WN, Hanna B. Time to detection of Mycobacterium tuberculosis in sputum culture correlates with outcome in patients receiving treatment for pulmonary tuberculosis. Chest 1998 Feb;113(2):379-386.
5. Vidal R, Martin-Casabona N, Juan A, Falgueras T, Miravitlles M. Incidence and significance of acid-fast bacilli in sputum smears at the end of antituberculous treatment. Chest 1996 Jun;109(6):1562-1565.
6. Singla R, Osman MM, Khan N, Al-Sharif N, Al-Sayegh MO, Shaikh MA. Factors predicting persisting sputum smear positivity among pulmonary tuberculosis patients 2 months after treatment. Int. J Tuber Dis 2003;7:58-64.
7. Ministry of Health. Diagnosis and treatment in 'STOP TB manual' TB Control Programme - Tuberculosis manual MOH Oman 2007 p. 10-19.
8. Rieder HL. Sputum smear conversion during directly observed treatment for tuberculosis. Tuber Lung Dis 1996 Apr;77(2):124-129.
9. World Health Organization. Treatment of tuberculosis: guidelines for national programmes. Geneva: WHO, 2000 2nd ed. WHO/CDS/TB/2000.275.
10. Mfinanga GS, Ngadaya E, Mtandu R, Mutayoba B, Basra D, Kimaro G, et al. The quality of sputum smear microscopy diagnosis of pulmonary tuberculosis in Dar es Salaam, Tanzania. Tanzan Health Res Bull 2007 Sep;9(3):164-168.
11. Lawson L, Yassin MA, Ramsay A, Olajide I, Thacher TD, Davies PD, et al. Microbiological validation of smear microscopy after sputum digestion with bleach; a step closer to a one-stop diagnosis of pulmonary tuberculosis. Tuberculosis (Edinb) 2006 Jan;86(1):34-40.
12. Liu Z, Shilkret KL, Ellis HM. Predictors of sputum culture conversion among patients with tuberculosis in the era of tuberculosis resurgence. Arch Intern Med 1999 May;159(10):1110-1116.
13. Saceanu CA, Pfeiffer NC, McLean T. Evaluation of sputum smears concentrated by cytocentrifugation for detection of acid-fast bacilli. J Clin Microbiol 1993 Sep;31(9):2371-2374.
14. Wilkinson D, Bechan S, Connolly C, Standing E, Short GM. Should we take a history of prior treatment, and check sputum status at 2-3 months when treating patients for tuberculosis? Int J Tuberc Lung Dis 1998 Jan;2(1):52-55.
15. Han JP, Sun SL, Li RZ, Zhang FS, Wang SC, Cheng J, et al. The short-term and long-term treatment outcomes in patients with pulmonary tuberculosis positive for drug-resistant and sensitive strains. Zhonghua Jie He He Hu Xi Za Zhi 2003 Feb;26(2):70-73.
16. Gopi PG, Chandrasekaran V, Subramani R, Santha T, Thomas A, Selvakumar N, et al. Association of conversion & cure with initial smear grading among new smear positive pulmonary tuberculosis patients treated with Category I regimen. Indian J Med Res 2006 Jun;123(6):807-814.
17. Rieder HL. Sputum smear conversion during directly observed treatment for tuberculosis. Tuber Lung Dis 1996 Apr;77(2):124-129.
18. Kumaresan JA, Ahsan Ali AK, Parkkali LM. Tuberculosis control in Bangladesh: success of the DOTS strategy. Int J Tuberc Lung Dis 1998 Dec;2(12):992-998.
19. Tahir M, Sharma SK, Rohrberg DS, Gupta D, Singh UB, Sinha PK. DOTS at a tertiary care center in northern India: successes, challenges and the next steps in tuberculosis control. Indian J Med Res 2006 May;123(5):702-706.
20. Harries AD, Gausi F, Salaniponi FM. When are follow-up sputum smears actually examined in patients treated for new smear-positive pulmonary tuberculosis? Int J Tuberc Lung Dis 2004 Apr;8(4):440-444.
21. Balasubramanian R, Garg R, Santha T, Gopi PG, Subramani R, Chandrasekaran V, et al. Gender disparities in tuberculosis: report from a rural DOTS programme in south India. Int J Tuberc Lung Dis 2004 Mar;8(3):323-332.
22. Arora VK, Singla N, Sarin R. Profile of geriatric patients under DOTS in Revised National Tuberculosis Control Programme. Indian J Chest Dis Allied Sci 2003 Oct-Dec;45(4):231-235.
23. Lienhardt C, Manneh K, Bouchier V, Lahai G, Milligan PJ, McAdam KP. Factors determining the outcome of treatment of adult smear-positive tuberculosis cases in The Gambia. Int J Tuberc Lung Dis 1998 Sep;2(9):712-718.
24. Güler M, Unsal E, Dursun B, Aydln O, Capan N. Factors influencing sputum smear and culture conversion time among patients with new case pulmonary tuberculosis. Int J Clin Pract 2007 Feb;61(2):231-235.
25. Al-Lawati JA, Mohammed AJ, Al-Hinai HQ, Jousilahti P. Prevalence of the metabolic syndrome among Omani adults. Diabetes Care 2003 Jun;26(6):1781-1785.
26. Singla R, Khan N, Al-Sharif N, Ai-Sayegh MO, Shaikh MA, Osman MM. Influence of diabetes on manifestations and treatment outcome of pulmonary TB patients. Int J Tuberc Lung Dis 2006 Jan;10(1):74-79.
27. Singh KJ, Ahluwalia G, Sharma SK, Saxena R, Chaudhary VP, Anant M. Significance of haematological manifestations in patients with tuberculosis. J Assoc Physicians India 2001 Aug;49:788, 790-794.
28. Domínguez-Castellano A, Muniain MA, Rodriguez-Baño J, Garcia M, Rios MJ, Galvez J, et al. Factors associated with time to sputum smear conversion in active pulmonary tuberculosis. Int J Tuberc Lung Dis 2003 May;7(5):432-438.
29. Perlman DC, el-Sadr WM, Nelson ET, Matts JP, Telzak EE, Salomon N, et al; The Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). The AIDS Clinical Trials Group (ACTG). Variation of chest radiographic patterns in pulmonary tuberculosis by degree of human immunodeficiency virus-related immunosuppression. Clin Infect Dis 1997 Aug;25(2):242-246.