Predictors of treatment failure among pulmonary tuberculosis patients in Mulago hospital, Uganda

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Abstract

Introduction: Early identification of Tuberculosis (TB) treatment failure using cost effective means is urgently needed in developing nations. The study set out to describe affordable predictors of TB treatment failure in an African setting.

Objective: To determine the predictors of treatment failure among patients with sputum smear positive pulmonary TB at Mulago hospital. The study was carried out in the TB clinic of Mulago hospital Kampala, Uganda.

This was an unmatched case control study where fifty patients with a diagnosis of TB treatment failure (cases) and 100 patients declared cured after completing anti TB treatment (controls) were recruited into the study. Cases were compared with controls to determine predictors of treatment failure.

Results: Significant predictors of treatment failure in this study included a positive sputum smear at 2 months of TB treatment (OR 20.63, 95%CI 5.42- 78.41) and poor adherence to anti TB treatment (OR 14.59, 95%CI 3.04-70.15).

Conclusion: This study identified a treatment related and a simple laboratory predictor of TB treatment failure in Mulago hospital which may be used in resource limited settings for early recognition of those at risk and early intervention.

Key words: Predictors; Treatment failure; Pulmonary TB

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Introduction

The control of tuberculosis (TB) remains a challenge globally,[1,2] more so in sub-Saharan Africa[2] and in high burden countries like Uganda where treatment target goals have not yet been met.[2] For TB control, the highest priority is to detect at least 70% of the sputum smear positive cases and to cure at least 85% of the sputum smear positive cases. If these targets are achieved, there is a decrease in prevalence, incidence, transmission and drug resistance to TB.[3]

Treatment failure of TB, which is defined as a patient who is sputum smear or sputum culture positive at 5 months or later after the initiation of anti TB treatment,[3] is one of the threats to the control of TB. This is because of its association with Multi Drug Resistant TB (MDR TB)[4] and also because affected patients continue to spread TB. Patients with treatment failure have a higher morbidity and mortality compared to those who achieve cure.[5] The World Health Organization (WHO) recommends diagnosis of TB treatment failure in resource limited settings by sputum smear microscopy at 5 months or later during treatment.[3] However, identification of those at risk of treatment failure is important before the 5 months in reducing TB spread, morbidity and mortality in affected individuals and may help in contributing to the achievement of the treatment targets. The ideal tool for this is frequent laboratory monitoring using sputum microscopy or culture. However, culture is not feasible in many settings with limited laboratory" resources like most of Uganda.[2]

Given these constraints there is need to obtain more easily measurable surrogate markers that may serve as predictors of TB treatment failure. Those patients identified to have the predictors of TB treatment failure may be prioritized for the use of limited laboratory resources. Studies done in other settings show that these predictors include social, radiological, laboratory and treatment related factors.[4,6-20] No study had been done in our setting to identify these predictors and we did a case control study to identify them.

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Methods

Ethical considerations

The study was approved by the Makerere University Faculty of Medicine Research and Ethics Committee. All participants gave written informed consent to participate. Assent was obtained from those who were under 18 years of age, in addition to the consent of their parents or guardians.

Study site

The study was conducted between June and December 2007 at Uganda's main national referral hospital of Mulago, in Kampala.

Study design and population

An unmatched retrospective case control study of the predictors of treatment failure among patients with sputum smear positive pulmonary TB was conducted.

Eligible patients thirteen years and above, with sputum smear positive TB at initiation of treatment and a positive sputum smear at 5 months or later after start of TB treatment were recruited. Controls were patients who were thirteen years of age and above, with sputum smear positive TB at initiation of treatment and had a negative sputum smear at 5 and 8 months after start of anti TB treatment.

Poor adherence was used to calculate the sample size since it is one of the most important predictors of treatment failure from previous studies. We used a level of poor adherence among treatment failure patients of 40% and 15% among patients who were cured.[21] Using the formula for comparison of proportions a minimum sample size of 120 subjects (40 cases, 80 controls) would be needed to achieve 80% power with a level of significance of 0.05[20] To increase the power of the study 50 cases and 100 controls were recruited

Study procedure

Data abstraction was done from medical records, patients' charts, and clinic cards in addition to interviewing patients. Those with incomplete records were excluded. A radiologist reviewed archived chest radiographs, which had been done at the time of diagnosis of TB. All data were recorded on a structured questionnaire. Information collected included age, gender, marital status, highest education level attained, approximate distance to the TB clinic, alcohol or substance abuse, fever persisting after 2 weeks of TB treatment, weight loss despite treatment or no weight gain, sputum smear microscopy results at baseline, 2 months and 5 months or later during treatment, drugs doses given and the presence of other medical conditions including HIV and Diabetes Mellitus (DM). All patients in this clinic were on the same treatment regimen, which is 2 months of rifampicin, isoniazid, ethambutol and pyrazinamide followed by 6 months of ethambutol and isoniazid.

Predictors of treatment failure were defined as factors which are associated with treatment failure and may be used to identify those at risk of treatment failure. These include socio-demographic, clinical, laboratory, radiological, and treatment associated factors.

Alcohol abuse was defined as a CAGE score of 2 and above[22]. Any weight gain or loss was calculated by subtracting the patients' weight at the start of TB treatment, from the weight at the time the patient was diagnosed with treatment failure or declared cured.

Results of the HIV test were obtained from the patients' medical records. All patients in the TB clinic are routinely counseled and tested for HIV. Random blood sugar was tested using a Glucometer (One Touch Ultra AW 060-368-13D Rev.03/2004, lifescan Inc. Milpitas, California Unites States of America). Diabetes Mellitus (DM) was defined as a random blood sugar of 200mg/dl and above in the presence of classic symptoms of hyperglycaemia.[23] Persistent fever was defined as fever lasting 2 or more weeks after initiation of anti TB treatment while a high bacillary load was defined as any sputum smear graded as having more than 10 acid alcohol fast bacilli per high power oil immersion field or grade +++ in the laboratory.

Adherence was assessed by taking a meticulous history to find out if patients missed any treatment and by asking them to estimate the duration of any treatment interruption. To minimize recall bias, adherence to treatment was crosschecked using the treatment card, which has space where patients or their relatives check after taking medication. Poor adherence was also assumed if the patients did not return for a scheduled appointment within a week of expected review on two or more occasions. Extensive radiological involvement was defined as lesion(s) involving an area of more than the equivalent of one lung with or without cavities.

Data analysis

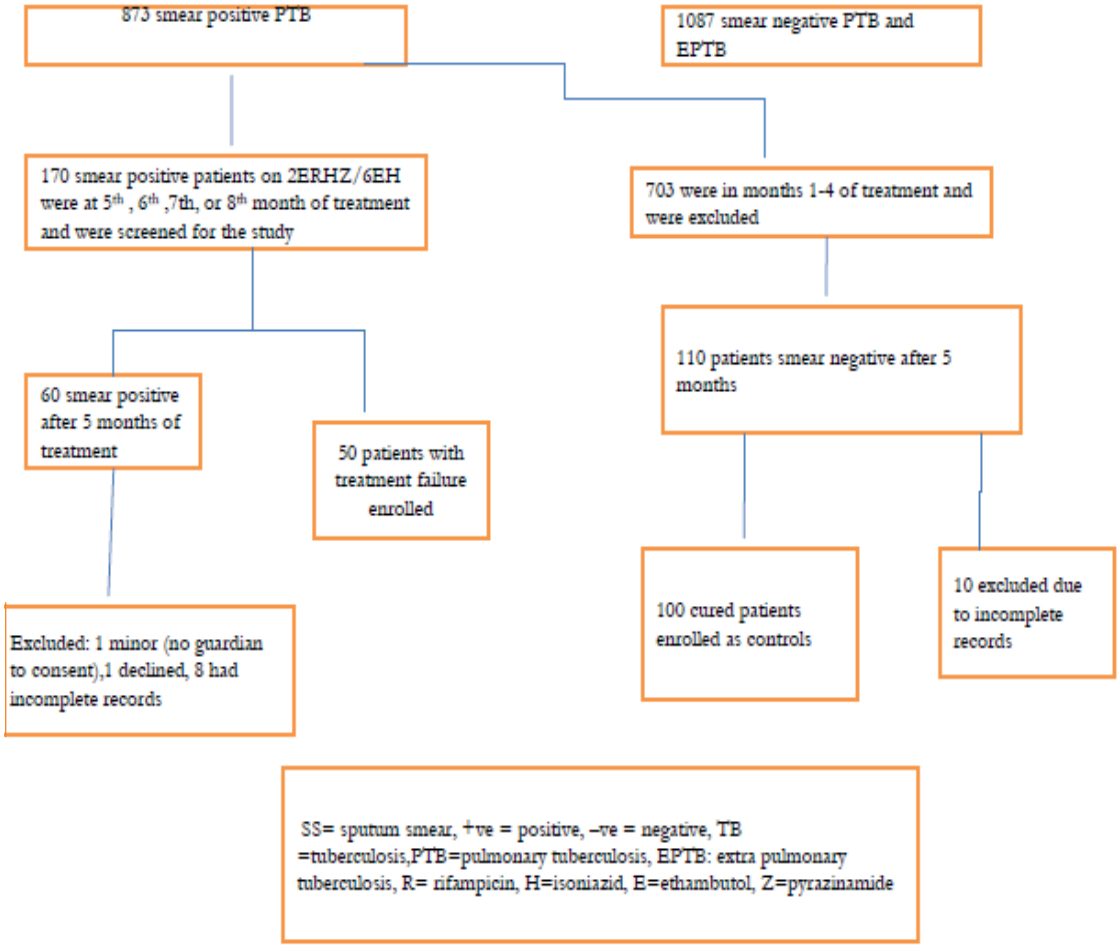
The data obtained was entered into Epi info 3.2.2 version, then exported to SPSS version 12.0 software for analysis.

Univariate analysis was performed to describe the baseline characteristics of the participants while bivariate analysis was performed to assess for possible associations between the individual predictor variables and the outcome predictor variable, which was TB treatment failure. Binary logistic regression using the backward elimination method was performed to determine the predictor variables while adjusting for confounding. The association between TB treatment failure and independent variables was assessed using odds ratios, 95% confidence intervals and p values. A p value of 0.05 or less was considered significant. The Chi-square tests were computed and the Fisher's exact test was used for cell frequencies less than five.

Results

Of the 1950 TB patients seen between June and December 2007, 873 had smear positive pulmonary TB while 1087 had either smear negative or extra pulmonary TB. For enrolment into the study, we considered the 170 of the smear positives who were at 5th, 6th, 7th, or 8th month of treatment. This yielded 60 smear positive patients after 5 months of treatment. Out of these, 50 were finally recruited as cases excluding 2 for consent related reasons and 8 for inadequate records. Out of the 170 smear positives we also considered 110 who had turned smear negative after five months as controls. We excluded ten for inadequacy of case records and finally recruited 100 controls as shown in figure 1.

Figure 1: Illustration of the study profile



Baseline characteristics

Baseline characteristics were comparable for cases and controls except distance from the clinic, with treatment failure cases significantly more likely to live further from the clinic than the controls (p= 0.0030, CI 1.07-4.34) as shown in Table 1.

Table 1: Baseline characteristics among cases and controls

Risk factors associated with treatment failure							
Cases (treatment failure N=50	%	Variable	Controls (cured) N=100	%	Unadjusted OR	P value	95% CI
		Age					
25	50	<32 years	58	58	0.72	0.330	0.37-1.43
25	50	>32 years	42	42	1.00		
		Gender					
33	66	Male	59	59	1.35	0.407	0.67-2.73
17	34	Female	41	41	1.00		
		Education level					
27	54	None or primary	47	47	1.32	0.419	0.67-2.62
23	46	Secondary or tertiary	53	53	1.00		
		Marital status					
26	52	Not married	65	65	0.58	0.124	0.29-1.16
24	48	Married	35	35	1.00		
		Alcohol abuse					
3	6	Yes	3	3	2.06	0.401	0.40-10.61
47	94	No	97	97	1.00		
		Distance to clinic					
24	48	>5km	30	30	2.15	0.030	1.07-4.34
26	52	≤5km	70	70	1.00		

Using bivariate analysis treatment failure cases were significantly more likely to have: persistent fever ($p<0.0001$), weight loss ($p<0.0001$), missed doses of treatment ($p= 0.002$), missed clinic appointments ($p<0.0001$), cavities on the baseline chest radiograph ($p< 0.0001$), extensive disease on the baseline chest radiograph ($p= 0.038$), a higher bacillary load at baseline ($p< 0.0001$) and positive sputum smear at 2 months of TB treatment ($p<0.0001$) as shown in table 2.

Table 2: The association between the different factors and treatment failure on bivariate analysis

Variable	Cases (treatment failure)		Controls (cured)		Unadjusted OR	P value	95% CI
	N=50	%	N=100	%			
HIV positive	21	42	50	50	0.72	0.355	0.37-1.44
Presence of DMBS ≥200mg/dl	2	4	0	0	*	0.050	*
Persistent fever	22	44	0	0	*	<0.0001	*
Weight loss	22	44	13	13	5.26	<0.0001	2.35-11.79
Distance to clinic > 5km	24	48	30	30	2.15	0.030	1.07-4.34
Missed doses> 2 weeks	21	42	18	18	3.30	0.002	1.55-7.05
Missed clinic appointments	22	44	6	6	12.31	<0.0001	4.55-33.34
Adverse effects of drugs	16	32	34	34	0.91	0.806	0.44-1.88
Insufficient dose for weight	4	8	4	4	2.09	0.304	0.50-8.72
Cavities on CXR at baseline	36	72	40	40	3.86	<0.0001	1.84-8.05
Extensive disease on CXR	32	64	46	46	2.09	0.038	1.04-4.19
High bacillary load at baseline (+++)	37	74	40	40	4.27	<0.0001	2.02-9.01
Positive sputum smear at 2 months	36	72	6	6	40.29	<0.0001	14.37-112.92

*Not calculated as one of the cells had zero so could not be cross-tabulated or computed

+++ = more than 10 acid alcohol fast bacilli per high power oil immersion field, CXR= chest radiograph

Binary logistic regression using the backward elimination method was done to control for confounding. All the factors that were statistically significant during bivariate analysis, plus potential confounders, were entered into a model for multivariate analysis. Predictors of treatment failure by multivariate analysis included a positive sputum smear at 2 months of TB treatment (OR 20.63, 95%CI 5.42- 78.41) and poor adherence to anti TB treatment (OR 14.59, 95%CI 3.04-70.15) as shown in Table 3.

Table 3: Association between the different factors and treatment failure on multivariate analysis

Variable	Unadjusted OR	95% CI	P value	Adjusted OR	95% CI	P value
Positive sputum smear at 2 months	40.27	14.37-112.91	<0.0001	20.63	5.42-78.41	<0.0001
Missed clinic appointments	12.31	4.55-33.34	<0.0001	14.59	3.04-70.15	0.001
Cavities on CXR at baseline	3.86	1.84-8.05	<0.0001	3.02	0.84-10.80	0.090
Distance to clinic > 5km	2.15	1.07-4.34	0.030	2.26	0.63-8.03	0.210
Fever> 2weeks	*	*	<0.0001	*	*	0.998
Sputum smear at baseline	4.27	2.02-9.01	<0.0001	0.48	0.11-2.18	0.34
Presence of DMBSe ≥200mg/dl	*	*	0.050	1.00	*	*
Weight loss	5.26	2.35-11.79	<0.0001	1.135	0.15-8.68	0.99
Missed doses	3.30	1.55-7.05	0.002	0.67	0.16-16.67	1.64
Extensive disease on CXR	2.09	1.04-4.19	0.038	0.77	0.29-5.13	1.23

+++ = more than 10 acid alcohol fast bacilli per high power oil immersion field,
CXR = chest radiograph, DM= diabetes mellitus, BS= blood sugar
*Not calculated due to small numbers in some cells

Discussion

This study examined socio-demographic, clinical, radiological, laboratory and treatment related factors associated with treatment failure in the TB clinic in Mulago hospital, Kampala. We found that a positive sputum smear at 2 months of anti TB treatment and poor adherence to anti TB treatment were predictors of treatment failure. None of the socio-demographic factors was associated with TB treatment failure in our study. Living further from the TB clinic had earlier been found to be associated with treatment failure by Shargie et al in 2007 in Ethiopia (HR 2.97, p<0.001)[24]. This may be due to failure to return for drug refills because of the longer distance, leading to poor adherence. In our setting the effects of this factor could have been masked by presence of various TB clinics within the city. Our study did not find alcohol abuse, lower level of education and male gender to be risk factors for TB treatment failure contrary to studies elsewhere[7, 8]. There may be other socio-cultural characteristics among our population that blunted any differences. Clinical factors previously described by other authors as risk factors for TB treatment failure including Diabetes Mellitus[8], persistent fever[9], weight loss[10,11] and HIV[12] seropositivity were not significant in our study.

A positive sputum smear at 2 months of TB treatment was found to be the strongest predictor of treatment failure in our study. This is in agreement with Chavez et al's finding in Peru (OR 1.7, p=0.008) [6]. This is an important observation since sputum microscopy is a low cost investigation and that can be used by TB programs to identify those at risk for early intervention. The first 2 months of TB treatment is when there is rapid killing of actively dividing bacilli and the semi-dormant bacilli. The majority of sputum smear positive patients turn negative within this period[3]. It is possible that a positive sputum smear at 2 months is due to primary drug resistance or alternatively, selection of mutant strains leading to MDR TB and treatment failure especially in the context of poor adherence[25]. This emphasizes the recommendation by TB programs to prolong the intensive phase if the sputum smear is positive at 2

months[3]. A high bacillary load at baseline was not associated with treatment failure in this study contrary to findings by Singla et al ($p<0.001$).[13] These differences could be accounted for by the higher rate of default on treatment among those who had a higher bacillary load and the intermittent regimen used in Singla's study.[13] It is noteworthy that Keane et al who used a treatment regimen similar to ours did not find high bacillary load at start of treatment a predictor of treatment failure.[11] Presence of cavities on the chest radiograph and extensive radiological involvement were not found to be significantly associated with treatment failure at multivariate analysis contrary to what was demonstrated by Qing-song et al (OR 1.5, $p=<0.001$)[14] This was probably due to inadequate sample size. Poor adherence to treatment was also a predictor of treatment failure in our study. This is in agreement with findings of Morsy et al [8] (OR 1.4, $p<0.05$), Burman et al[15] (RR 9.9, $p<0.001$) and Diel et al [16] ($p<0.001$). Poor adherence leads to development of drug resistance which may explain the treatment failure. Given these findings, program interventions like Directly Observed Therapy short course (DOTS), which enhance adherence, should be emphasized.

Conclusion

Positive sputum smear at 2 months of TB treatment and poor adherence to anti TB treatment were found to be predictors of TB treatment failure in Mulago Hospital. These factors may be used in resource limited settings for early recognition of those at risk and early intervention.

Recommendations

The National TB programs should emphasize the recommendation of sputum microscopy at 2 months of treatment to detect those at risk so that they can be followed up closely. Patients with poor adherence to treatment should be closely followed up to prevent treatment failure. Studies need to be done to find out the effect of prolonging the intensive phase of treatment in those with positive sputum smears at 2 months.

Limitations of the study

Culture and sensitivity of TB was not done for controls so it was difficult to tell if drug resistance was a predictor of treatment failure.

Some patients were excluded because they were missing important data in their records. This may have introduced bias if having missing records is related to certain risk factors.

The definition of treatment failure used was the one recommended by WHO for resource limited settings and therefore sputum culture was not used in the definition, which could have led to misclassification of cases and controls. Serum drug levels to quantify adherence were not feasible in our study. The sample size was inadequate as shown by the wide confidence intervals and therefore some predictors with lower odds ratios could have been missed.

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References

1. World Health Organization (WHO) fact sheet No 104. Revised March 2007:1-3. http://www.who.int/mediacentre/factsheets/fs104/en/. last accessed on 5/050/09.
2. Profiles of High burden countries. WHO Report 2007, Global Tuberculosis control, surveillance, planning, financing. Annex 1:145-148. http://www.who.int/tb/publications/global_report/2009/pdf/chat1.pdf. Last accessed
3. Harries A, Maher D and Graham S. Management of patients with tuberculosis. In: TB/HIV a clinical manual, Geneva: World Health Organisation. p.111-115.
4. Becerra MC, Freeman J, Bayona J, et al. Using treatment failure under effective directly observed short course chemotherapy programme to identify patients with Multi drug resistant tuberculosis. *Int J Tuberc Lung Dis*. 2000; 4:108-114.
5. Sadacharam K, Gopi P, Chandrasekaran S, et al. Status of smear TB patients at 2-3 years after initiation of treatment under a DOTS programme. *Ind J Tuberc*. 2007; 54:199-203.
6. Chavez Pachas AM, Blank R, Smith Fawzi MC, Bayona J, Becerra MC and Mitnick CD. Identifying early treatment failure on category I therapy for pulmonary tuberculosis in Lima Ciudad, Peru. *Int J Tuberc Lung Dis*. 2004; 8:52-58.
7. de Albuquerque M de F, Ximenes RA, Lucena S et al. Factors associated with treatment failure, drop out, and death in a cohort of tuberculosis

patients in Recife, Pernamubuco State,Brazil. *Cad Saude Publica*.2007; 23:1573-1582.
8. Morsy AM, Zaher HH, Hassan MH and Shouman A. Predictors of treatment failure among tuberculosis. Patients under DOTS strategy in Egypt. *East Mediterr Health J*. 2003; 9:689-701.
9. Kiblawi SS, Jay SJ, Stonehill RB, et al. Fever response of patients on therapy for pulmonary tuberculosis. *Am Rev Respir Di*s.1981; 123: 20 – 24.
10. Rossana A, Ditangco, Melchor C, et al. Clinical predictors of response to tuberculosi chemotherapy. *Philippine Journal of Microbiology and Infectious Diseases*. 1996;25:1820.
11. Keane VP, de Klerk N, Krieng T, Hammond G and Musk WA. Risk factors for the development of non-response to first line treatment for tuberculosis in Southern Vietnam. *Int J Epidemiol*.1997; 26:1115-1120.
12. Perriens JH, Colebunders RL, Karahunga C, et al. Increased mortality and tuberculosis treatment failure rate among HIV seropositive compared with HIV sero-negative patients with pulmonary tuberculosis treated with 'standard' chemotherapy in Kinshasa, Zaire. *Am Rev Respir Dis*.1991; 144:750-755.
13. Singla R, Singla N, Sarin R and Arora V.K. Influence of pre-treatment bacillary load on treatment outcome of Pulmonary Tuberculosis patients receiving DOTS under revised National Tuberculosis Control Programme. *Ind J Chest Dis Allied Sci*. 2005; 47:1923.
14. Qing-Song Bao, Yu-Hua Du, Ci-Yong Lu. Treatment outcome of new pulmonary tuberculosis in Guangzhou, China, 1993-2002: a register–based cohort study. *BMC Public Health*. 2007; 7:344.
15. Burman WJ, Cohn DL, Reitmeijer CA, Judson FN, Sbarbaro J A and Reves RR. Non ompliance with directly observed therapy for tuberculosis. Epidemiology and effect on the outcome of treatment. *Chest*. 1997; 111:1168-1173.
16. Diel R, Niemann S. Outcome of tuberculosis treatment in Hamburg: a survey,1997 2001. *Int J Tuberc Lung Di*s.2003; 7:124-131.
17. Jindani A, Nunn A, Earson D. Two-8month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis. *Lancet*. 2004;364:1244-1251.
18. Jindal SK. Antituberculosis treatment failure in clinical practice. *Ind J Tub*.1997; 44: 121-124.19.
19. Manmoudi A, Iseman M. Pitfalls in the care of patients with Tuberculosis. Common errors and their association with the acquisition of drug resistance. *JAMA*.1993; 270:65-68.
20. Stephen Hulley, Steven Cummings, Warren Browner Designing Clinical Research Lipincott Williamsssss and Wilkins Second Edition Chapter 6 page 87 ISBN 0781722187.
21. Johnson JL, Okwera A, Vjecha MJ, et al. Risk factors for relapse in Human Immunodeficiency virus type 1 infected adults with pulmonary tuberculosis. *Int J Tuberc lung Dis*.1997 Oct; 115:446-453.
22. Marc Ghany, Jay h. Hoofnagle *A*pproach to the Patient with Liver Disease in Harrisons Principles and Practice of Medicine. The McGraw-Hill Companies, Inc. 2005 Edition page 1808-1822
23. Alberti KG, Aschner PA, Assal J P, et al. Definition, diagnosis and classification of Diabetes Mellitus and its complications. Report of a World Health Organization (WHO) consultation, WHO, 1999. Downloaded at http://www.staff.ncl.ac.uk/philip.home/who_dmc.htm on 02/02/09 .
24. Shargie E, Lindtjorn B. Determinants of Treatment Adherence among Smear-Positive Pulmonary tuberculosis patients in Southern Ethiopia. *PLoS Med*.2007; 4:e37
25. Mitchison DA. How drug resistance emerges as a result of poor compliance during short course chemotherapy for tuberculosis. *Int J Tuberc Lung Dis*. 2002; 2:10-15.