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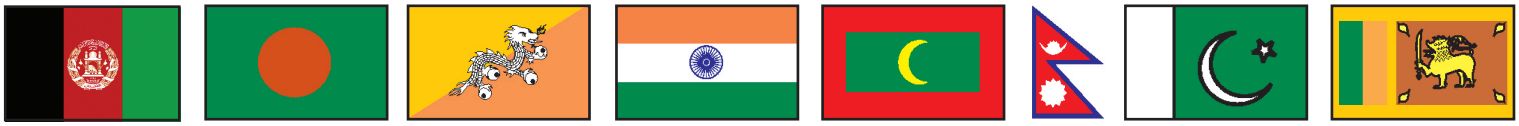

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Address:

SAARC Tuberculosis and HIV/AIDS Centre,
Thimi, Bhaktapur,
G.P.O. Box 9517
Tel: 00977-1-6631048, 6632601, 6632477
Fax: 00977-1-6634379
E-mail: saarctb@mos.com.np
Website: www.saarctb.com.np

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Fax: 00977-1-6634379
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Use double spacing throughout, including title, abstract, text, acknowledge, reference, table and legends for illustrations. Begin each of the following sections on a separate paper. Number pages consecutively.

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Editorial

This issue of STC journal contains main articles on gender issues in TB control. TB is a communicable disease, which affects human beings, however the impact of disease is different among male and female. More cases are reported among men but the fatality rate remains high in women. TB kills more women than all combined causes of maternal mortality, so TB is called one of the leading killers among women. Another major factor for death of women from TB is co-infection with HIV. Male female ratio of more than one was observed among TB suspects undergoing sputum examination in SAARC Member States except in Pakistan where it was less than one. In Nepal the sputum positivity rate was similar in male and female. Males are more affected as new sputum smear positive as well as negative pulmonary tuberculosis than female, where as in extra pulmonary tuberculosis female are more affected than male. Regarding the gender distribution of cured and treatment failure it is found to be similar in male and female, where as in relation to defaulter and died, males are more affected than females. Higher number of female TB suspects were found in female in the age group 15-19 years and beyond that males were more. Compare to males higher number of females complained of fever, chest pain and loss of appetite. Reports of TB cases suggest, virtually in all countries of SAARC, fewer female than male TB cases are notified. Among TB patients it is reported that males are more in labors and females much more in housework. Major portion of male TB patients identify themselves as the main source of income for their household. The expenditures attributable to consultation, diagnosis and medication of tuberculosis for male and female patients accounted lesser than of the mean monthly income for males than for females.

Community based epidemiological studies have established that males have a higher prevalence of TB infection and a higher rate of progression from infection to active disease than females. Yet there are underreported due to various socio-cultural factors. Moreover, profound gender differential existing in SAARC Member States may create barriers for women in seeking health care leading to under reporting of female TB cases in this region. Information regarding TB disease is different among male and female because of its culture values, social norms etc. More study on gender related TB is very vital in National TB control program and it should be encouraged.

A DIAGNOSTIC TOOL TO SCREEN FOR HIV CO-INFECTION AT THE TB DOTS CENTRE IN INDIA

Rajasekaran,[1] L. Jeyaseelan,[2] A. Mahilmaran,[1] O.R. Krishnarajasekhar,[1] S. Kumar MD,[1] S. Annadurai[1]

1Government Hospital for Thoracic Medicine, Tambaram Sanatorium, Chennai, India.2
[2]Department of Bio statistics, Christian Medical College, Vellore, India

Abstract

Setting: Government Hospital for Thoracic Medicine (GHTM), a referral hospital for TB and HIV/AIDS in south India.

Objective: HIV is the most important risk factor for causing TB. In settings where HIV tests are not routinely available, patients with TB might not be referred for HIV testing. To evaluate the role of a simple diagnostic tool to screen for HIV at the DOTS center in India.

Method: Cross sectional study of TB and HIV patients using electronic medical records. The patients visited from January 2003 to September 2004 were included for study. Out of 15,326 consecutive TB patients 6791 (44.3%) were HIV positive. Signs and symptoms in relation to HIV/AIDS during their first visit were obtained. Chi square test and logistic regression were used to develop a scoring system to determine which TB patients were most likely to be co-infected with HIV. Bootstrap and prospective evaluation were done to validate the models.

Results: Factors associated with increased risk for HIV were diarrhea, oral thrush, itching and absence of haemoptysis, sputum, and age <40 years. The scoring system based on these factors provided 90% sensitivity and 64% specificity. An alternate scoring system without haemoptysis provided 91% sensitivity and 58% specificity.

Conclusion: This diagnostic tool could be used to screen patients for HIV at DOTS centers in high prevalence areas and refer them to VCT centre for testing.

Keywords: TB and HIV co-infection, diagnostic tool, scoring system.

Introduction

Human Immunodeficiency Virus (HIV) infection poses tremendous challenges to health globally. The number of people living with HIV in 2005 was 40.3 million and over 90% of them live in resource poor countries.[1] India is in the midst of HIV and AIDS crisis, with over 5.1 million infected people, the second highest burden in the world after South Africa. In India, the HIV prevalence in adults estimated through the national antenatal clinic surveillance program was 0.91% in 2004.[2] At the same time, tuberculosis (TB) is another health problem of global significance. The rising number of TB cases can be attributed to increasing poverty, non-compliance with TB control programs, a growing population, and the spread of HIV. TB has become the most important opportunistic infection and among the major causes of death among HIV patients in Africa. The rate of HIV infection among tuberculosis patients was much higher than the rate of infection in the general population. This was reported to be 75% among tuberculosis patients in Malawi in 1993-94 and 73% in Zambia in 1988-96.[3] In

Correspondence to:
Dr. S. Rajasekaran MD
Superintendent
Government Hospital for Thoracic Medicine
Tambaram, Chennai - 600047,India.
Email: rajasekaran.s@ghtm.com

India, there were evidences to show spurt in HIV-TB co-infection cases in both the rural[4] and urban TB clinics.[5, 6] In order to control the epidemic, number of countries implementing the Directly Observed Treatment Strategy (DOTS) for TB control are increasing year by year, and the proportion of world's TB patients treated under the DOTS has increased from 7% in 1994 to 27% in 2000.[7] According to Faussett *et al* (2002), while HIV infection is fuelling the tuberculosis (TB) epidemic, the TB programmes have focused only on TB case finding and treatment, with little attention to HIV / AIDS interventions. Although TB is a leading cause of HIV related morbidity, HIV/ AIDS programmes were generally paid little attention to TB. Thus, despite close epidemiological links between HIV and TB, the public health responses have largely been separate.[8]

While UNAIDS suggested a policy for HIV testing[9] at present in India there is no national policy regarding testing for HIV among patients being treated for TB. Because of the cost of testing, stigma, and the vertical nature of AIDS Control programme, universal testing of DOTS patients for HIV is unlikely in the near future. In India the DOTS programme has been well rooted in the community. The case finding, treatment and referrals have been well monitored and evaluated periodically. Therefore, it is strategically feasible to target the linkages between HIV and TB in the DOTS centres. TB being the leading cause of HIV/AIDS related illness and death, there is a need for simple diagnostic tools and drugs to slow the progress of the TB epidemic.[10] This paper evaluates the role of a simple diagnostic screening tool which could be used at DOTS centres in India to identify those most likely to be infected with HIV.

Methods

Government Hospital of Thoracic Medicine (GHTM): Created as a tuberculosis sanatorium in 1928, and renamed as the Government Hospital of Thoracic Medicine (GHTM) in 1980, the hospital is a premier treatment and a referral centre for TB and HIV/AIDS with 776 bedded in-patient treatment facilities. In 1992 the hospital admitted its first two patients with HIV/ AIDS. Twelve years later in 2004, 28,700 HIV patients utilized the services at the hospital. GHTM, Tambaram is the largest voluntary counselling and testing centre, comprehensive prevention, care and support centre for persons living with HIV/AIDS (PLHAs) in south India. Outpatient management of PLHAs includes treatment for opportunistic infections, immuno-restorative indigenous Siddha drug formulations and prophylaxis for *Pneumocystis carinii* pneumonia. Patients having advanced HIV disease with various complications receive hospitalised care in 11 wards. There is a separate palliative care ward for the needy patients. Free anti-retroviral therapy (ART) is being given to the eligible PLHAs, as part of National AIDS Control Programme, since April 1, 2004 and as on December 31, 2005, a total of 2,330 patients had started ART therapy at the GHTM ART centre.

TB and HIV Hospital Information System (T/HIS): In order to improve the quality of patient care and to provide a system to track trends over time, an electronic medical record system was developed. The software called the TB/HIV Information system (THIS) was designed to meet the unique needs of "outpatient" and "inpatient" care provided at this hospital. The information system was launched in December 2001 and had been modified to meet the changing needs of the institution. Patients are provided with unique patient numbers that are maintained in the confidential data system. Patient information is tracked during the follow up visits. Data collected at the out patient counters, inpatient services, laboratory, VCTC and ART facilities are linked for a comprehensive dataset.

Statistical Methods: Data on demographic characteristics together with signs and symptoms in relation to HIV/AIDS on first visit were analysed to determine which occurred more commonly in TB patients with HIV than in TB patients without HIV. A two-step process was used. All signs and symptoms were screened for possible association with HIV using a chi-square test with Yates correction and /or Fisher's exact test. Then those symptoms found to be associated with HIV were analysed using multiple logistic regression to determine the joint association between the various factors. All symptoms except depression, which is difficult to evaluate in the DOTS centres, were then included in the multiple logistic regression analysis. Stepwise method was used to identify significant variables. The assumptions underlying logistic regression were validated graphically using the residuals versus predicted probability. SPSS 11.5 and STATA 8.0 were used to analyse the data.[11]

Scoring Systems: The presence or absence of symptoms that had the odds ratio (OR) ≥ 3 in the logistic regression model were used to develop the scoring systems. The OR was used rather than the p-value for the various terms to best identify symptoms that would discriminate large numbers of HIV infected and uninfected patients well. There were five symptoms, together with age, that had odds ratios >3. For the first scoring system (called model A), the five symptoms with odds ratios >3 and age were given equal weight of 1, which is the score computed for each patient by counting the presence of selected symptoms. Therefore, the minimum and maximum score were 0 and 6 respectively. Absence of sputum was excluded in the second scoring system (called model B), giving possible scores between 0 and 5 inclusive. For each system, the distribution of scores by the diagnosis was divided at various cut off points and the sensitivity, specificity and positive predictive values were calculated. The Receiver Operating Characteristic (ROC) curve was drawn to decide the best cut off point. The point, which provided high sensitivity and good specificity, was chosen as the best cut off point. Other models representing different combinations of the 6 variables were also evaluated, but none performed as well as the two systems used presented here.

Prospective Validation: The consecutive patients who had come to the GHTM for the following three months (October 1, 2004 to December 31, 2004), whose TB diagnosis and HIV test were done at GHTM were considered to validate the scoring system. Using the symptoms and signs for these patients, they were scored by Model A and Model B, and the results compared with their HIV findings.

Confidence Intervals: The patient data used to develop the scoring systems were re-sampled with replacement for 1000 times. The values for the sensitivity and specificity for the selected cut off point was documented for each sample. The 2.5th and 97.5th percentiles of the sensitivity and specificity from the 1,000 bootstrap samples determined the 95% confidence intervals.

Results

A total of 128,094 patients visited, for the first time, at out-patient department of the Government Hospital for Thoracic Medicine (GHTM) from January 1 2003 to September 30, 2004. Of these patients, 21,365 diagnosed with HIV and 21,098 were diagnosed and confirmed by laboratory testing to have TB. All the confirmed TB patients, 15,326 were tested for HIV. Among them 6,791 were HIV positive (TB-HIV) and 8,535 HIV negative (TB-only). Data on presenting symptoms for the TB-HIV and TB were used to develop the scoring systems.

The distribution of socio demographic characteristics of the TB patients is presented in table 1.

TB-HIV patients tended to be younger than TB-only patients. Of TB-HIV patients, 67% were between the age group of 25-39 years while only 28.7% of TB-only patients were in this age range (p<.001). The proportion of female patients was higher (p<.001) among the TB-HIV group (27.9%) than among the TB-only group, though the males were majority in both groups. Among the TB-HIV patients, there were more divorced patients than among TB-only patients (5.2% vs. 1.2%, p<.001). A higher proportion of TB-HIV patients were from neighbouring state of Andhra Pradesh than TB-only patients (45.6% vs. 4.8%, *p*<.001).

Table 1 Distribution of socio demographic characteristics of TB patients with and without HIV

Characteristics	TB with HIV (TB-HIV) (n = 6791)		TB without HIV (TB-only) (n = 8535)		p-value
	n	%	n	%	
Age					
≤ 14	279	401	170	2.0	
15 – 19	49	0.7	250	2.9	
20 – 24	511	7.5	505	5.9	
25 – 29	1536	22.6	668	7.8	
30 – 39	3015	44.4	1613	18.9	<.001
40 – 49	1067	15.7	1939	22.7	
50 & Above	334	4.9	3390	39.7	
Sex					
Male	4895	72.1	6716	78.7	<.001
Female	1896	27.9	1819	21.3	
Marital Status					
Married	5158	76.0	6887	80.7	
Divorced	351	5.2	100	1.2	<.001
Unmarried	1036	15.3	1254	214.7	
Widow or Widower	246	3.6	294	3.4	
State					
Tamil Nadu	3598	53.0	8088	94.8	
Andhra Pradesh	3098	45.6	413	4.8	<.001
Others	95	1.4	34	0.4	

The distribution of symptoms, OR and 95% CI by HIV status is presented in Table 2.

Nearly 18% of the TB-HIV patients had diarrhoea, which was significantly (p<.001)

Table 2 Distribution of Symptoms of TB patients by HIV status

Symptoms	TB with HIV (TB-HIV) (n = 6791)		TB without HIV (TB-only) (n = 8535)		OR	95% CI	p-value
	n	%	n	%			
Cough	3879	57.1	8220	96.3	0.05	0.04-0.06	.000
Fever	2635	38.8	3524	41.3	0.90	0.84-0.96	.002
Wt. Loss	1320	19.4	1100	12.9	1.63	1.49-1.78	.000
Diarrhoea	1168	17.2	161	1.9	10.8	9.13-12.8	.000
Sputum	3511	51.7	8126	95.2	0.05	0.05-0.06	.000
Haemoptysis	125	1.8	1122	13.1	0.12	0.10-0.15	.000
Chest Pain	747	11.0	1694	19.8	0.50	0.45-0.55	.000
Breathlessness	849	12.5	3255	38.1	0.23	0.21-0.25	.000
Wheeze	944	13.9	5670	66.4	0.08	0.07-0.09	.000
Body ache	1006	14.8	711	8.3	1.91	1.73-2.12	.000
Head ache	695	10.2	528	6.2	1.73	1.54-1.95	.000
Tiredness	1316	19.4	769	9.0	2.43	2.21-2.67	.000
Oral Ulcer	705	10.4	87	1.0	11.3	8.98-14.1	.000
Nausea Vomiting	588	8.7	213	2.5	3.70	3.16-4.35	.000
Pain Abdomen	816	12.0	304	3.6	3.70	3.23-4.24	.000
Painful Swallowing	255	3.8	59	0.7	5.60	4.21-7.45	.000
Itching	490	7.2	59	0.7	11.2	8.51-14.7	.000
Skin Lesions	215	3.2	17	0.2	16.4	9.98-26.9	.000
Depression	18	0.3	6	0.1	3.78	1.50-9.52	.005

higher than 2.0% of the TB-only patients (OR=10.8). Although the weight loss was significantly higher in the TB-HIV group (19.4%) as compared to the TB-only group (12.9%), the odds of weight loss were only 1.6 times higher. Body ache was significantly (p<.001) higher in the TB-HIV group as compared to TB-only group (OR=2). Similarly, headache and tiredness were significantly higher in the TB-HIV group as compared to TB-only group (OR 1.7 and 2.4 respectively). Oral thrush was significantly higher (p<.001) in the TB-HIV patients (OR=11) as were nausea/vomiting and pain in the abdomen (ORs of 3.7). Painful swallowing was also significantly (p<.001) higher in the TB-HIV group (OR=5.6). Finally the OR for itching and for skin lesions was high, but relatively few patients were present with these symptoms.

Other symptoms that presented significantly more often among TB-only patients as compared with the patients with TB-HIV co-patients were cough, fever, sputum, haemoptysis, chest pain, breathlessness and wheeze.

The results of logistic regression analysis using these signs and symptoms with odds ratios of 3 or greater are presented in table 3.

In the logistic regression analysis for symptoms, the diarrhoea was significantly (p<.001) higher in TB-HIV patients as compared to TB-only patients (OR=6.4). Similarly, oral ulcer, itching, skin lesion, pain in the abdomen, painful swallowing, fever, tiredness and body ache were significantly higher in TB-HIV group (odds ratios 5.5, 4.6, 2.0, 2.0, 1.9, 1.7, 1.6, and 1.2 respectively and the symptoms, i.e. up, that is, no wheeze or breathlessness, no haemoptysis, no sputum, and no chest pain were significantly higher in the TB group (odd ratios of 6.3, 4.9, 3.4, 2.4 and 1.3 respectively). Younger patients (£ 39 years) were significantly (p<.001) higher in the TB-HIV group.

The ROC curve based on the various cut off values of the score for the model A (age, diarrhoea, oral ulcer, itching, no haemoptysis and no sputum) and Model B (age, diarrhoea, oral ulcer, itching, and no haemoptysis) were derived by counting the presence of five symptoms and age, whose OR were greater than or equal to 3, is presented in figure 1a and 1b.

Table 3 Logistic Regression for association of symptoms with HIV

Symptoms	Adjusted Odds Ratio	95 % CI	p-value
Age (£ 39 Years)	4.3	3.88 – 4.72	.000
No Wheeze or Breathlessness	6.3	5.71 – 7.01	.000
No Haemoptysis	4.9	3.94 – 6.20	.000
No Sputum	3.4	2.76 – 4.27	.000
No Cough	2.4	1.93 – 3.10	.000
No Chest pain	1.3	1.12 – 1.46	.000
Diarrhoea	6.4	5.17 – 7.82	.000
Oral Ulcer	5.5	4.16 – 7.22	.000
Itching	4.6	3.23 – 6.64	.000
Skin Lesion	2.0	1.10 – 3.66	.024
Pain Abdomen	2.0	1.62 – 2.37	.000
Painful Swallowing	1.9	1.30 – 2.85	.001
Fever	1.7	1.50 – 1.82	.000
Tiredness	1.6	1.40 – 1.86	.000
Body Ache	1.2	1.07 – 1.45	.004

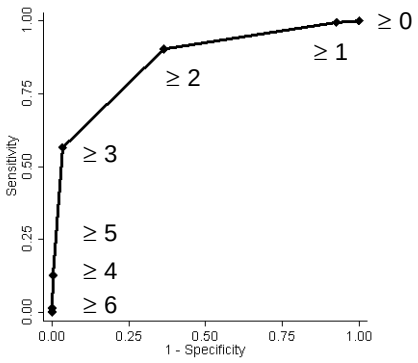

Figure 1a Receiver Operating Characteristics Curve for Model A

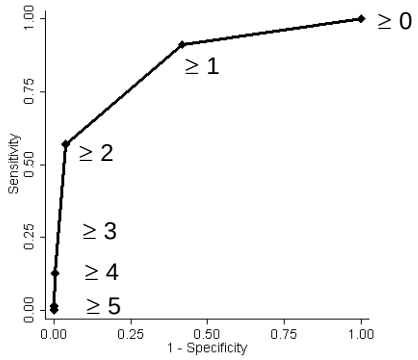

Figure 1b Receiver Operating Characteristics Curve for Model B

In model A, the cut off value ³ 2, provided 90% sensitivity and 64% specificity while the cut off value ³ 3 provided 57% sensitivity and 97% specificity. In model B, the cut off value ³ 1 provided 91% sensitivity and 58% specificity and the cut off value ³ 2 provided 57% sensitivity and 96% specificity. The area under the curve (AUC) for the model A was 0.86 while the AUC for model B was 0.85.

Prospective Validation: There were 3843 TB-HIV patients and 5022 TB-only patients seen at the hospital for the first time during the time period October 1 to December 31, 2004. The presence of 5 symptoms and age for model A and presence of 4 symptoms and age for model B, were counted for each patients, which was considered as score. Then the score was divided at ³ 2 for model A and ³ 1 for model B. The corresponding sensitivity, specificity, accuracy and predictive values are presented in table 4a and 4b.

Table 4b Distribution of Sensitivity, Specificity and 95% CI by Bootstrap and Prospective Validation methods for model B

Validity Statistics	Bootstrapping	Prospective validation 1st October to 31st December, 2004
Sensitivity (%)	91.2 (90.5 – 91.8)	92.7 (90.1 – 94.9)
Specificity (%)	58.3 (57.2 – 59.2)	41.8 (38.6 – 45.0)
Positive Predictive Value (%)		46.1 (43.0 – 49.2)
Negative Predictive Value (%)		91.5 (88.4 – 94.0)

Table 4a Distribution of Sensitivity, Specificity and 95% CI by Bootstrap and Prospective Validation methods for model A

Validity Statistics	Bootstrapping	Prospective validation 1st October to 31st December, 2004
Sensitivity (%)	90.4 (89.7 – 91.0)	91.7 (89.0 – 94.0)
Specificity (%)	63.6 (62.6 – 64.7)	48.4 (45.1 – 51.7)
Positive Predictive Value (%)		48.8 (45.6 – 52.1)
Negative Predictive Value (%)		91.6 (88.8 – 93.9)

Confidence intervals

The bootstrap confidence intervals for the sensitivity, specificity, accuracy and predictive values are presented in table 4a and 4b.

In model A, the prospective evaluation with the cut off of ≥ 2 provided sensitivity 90.4% (89.7 – 91.0) and specificity 48.4% (45.1 – 51.7). The positive and negative predictive values were 48.8% (45.6 – 52.1) and 91.6 (88.8 – 93.9) respectively. In the bootstrapping, at the same cut off level for model A, the sensitivity was 90.4% (89.7 – 91.0) and specificity was 63.6% (62.6 – 64.7).

In model B, the prospective evaluation with the cut off of ≥ 2 provided sensitivity 92.7% (90.1 – 94.9) and specificity 41.8% (38.6 – 45.0). The positive and negative predictive values were 46.1% (43.0 – 49.2) and 91.5 (88.4 – 94.0) respectively. In the bootstrapping, at the same cut off level for model B, the sensitivity was 91.2% (90.5 – 91.8) and specificity was 58.3% (57.2 – 59.2).

Discussion

TB is the commonest opportunistic infection in HIV infected persons. In India, it was estimated that 50-60% of HIV positive persons would develop TB in their life time.[2] The rate of HIV infection among the TB patients in Malawi during 1993-1994 and Zambia in 1988-96 was 75% and 73% respectively.[3] In our study the rate of HIV among TB patients was 44% during January 2003 to September 2004, while the rate of TB among HIV patients was 35%. The National AIDS Control Organization of India has reported occurrence of TB symptoms among HIV patients at a rate similar to the findings of the study.[2] However, studies reporting the symptoms, were commonly prevalent for HIV and TB patients, are scanty and the symptoms reported here would represent HIV/AIDS patients in south India.

In 2004 UNAIDS recommended universal screen for HIV among all TB infected patients seen at DOTS centres.[10] However for reasons discussed later, the recommendation has not been implemented in India. As an interim measure, before universal screening, we are recommending our scoring systems an easy method to determine which patients are most likely to be co-infected with HIV.

Clinical prediction rules, such as our scoring system, have been proposed as a way to increase the accuracy of clinical diagnosis. Most often these rules are cost effective and easy to use. These were developed to screen the patients as well as for predicting the outcome These are more suitable as a screening tool, when the programmes have prevention facilities at the Primary Health Centre levels.[10,12,13]

The predictive value of the scoring system depends on the underlying HIV prevalence in the population in which it is being used. In TB DOTS centres where there is a low rate of HIV among patients, the positive predictive value will be low. Therefore, a DOTS centre choosing the model to implement should have continuous feedback from Voluntary Counselling and Testing (VCT) centres to get sufficient data on HIV prevalence in that area. However, with the HIV epidemic advancing and maturing, more and more HIV seropositives would be presenting with TB as their immune systems being suppressed. Hence, we might expect of increasing the underlying HIV prevalence in the DOTS centres to increase and the positive predictive value of the index. Therefore, even if the yield is low now, a DOTS centre might be re-evaluating the use of the index every couple of years.

To illustrate, in the fourth quarter of 2004, 288,102 new TB patients were started on TB therapy in DOTS centres in India. If HIV prevalence among these patients were 5%, then we estimate using model A that slightly less than 40% would have been referred for testing. While the savings is significant compared to universal screening, the burden on existing VCT could be large. Additional resources may be required to support VCT in areas where prevalence is high.[14] To reduce the number referred, a higher cutoff point could have been chosen using model A. With e" 3 symptoms the number of patients referred would have been low (20,182 only). This might have resulted in lower detection of HIV among TB patients attending DOTS centres. Therefore, we are not recommending this cut off point.

There is a complimentary effort being promoted by WHO called the "Pro Test Initiative."[8] This initiative calls for increased screening TB in HIV counselling and testing centres. With our proposed scoring system use to promote HIV testing in TB centres, the overall health care system in a country would immensely benefit by identifying patients needing care from both HIV and TB service providers. Flykesnes *et al* (1999) reported that the readiness for Voluntary Counselling and Testing in the general population was very low and factors such as concerns about confidentiality and length of time waiting for the test result contributed to the low utilization rate.[15] However, in India, the TB program is well rooted and integrated. The prevalence of HIV in DOTS centres in India had been reported to be 5% on average. This may suggest about appropriation for universal screening for HIV for all TB patients. However, there are at least two reasons why this might not be the wisest. First, stigma associated with HIV is very high. If DOTS centres are directly associated with HIV screening then many TB patients may refuse to visit DOTS centre being fear of labelled as HIV positive.[16] Second, the staff members of well functioning DOTS

programs are already heavily burdened with tasks such as case finding, treatment and follow-up. Adding universal screening, with necessary counselling component would put extra burden on existing staff or there might be needed for hiring new staff, for which resources have not been made available. For both of these reasons, TB experts in India are not in favour of adding routine HIV screening at DOTS centres.

This study developed the scoring system based on the symptoms which could be used by community health workers and counsellors at the primary and secondary level care settings. Maher (2002) reported that the progress in slowing the TB epidemic depends on the effectiveness of the tools available (drugs, diagnostics and vaccines) and the extent to which they are put into use. The proposed tool is simple, effective and easy to use. However, the scoring system needs to be prospectively evaluated at the field level in order to refine well.

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GENDER DISPARITY AMONG TB SUSPECTS & NEW TB PATIENTS

A RECORD-BASED RETROSPECTIVE STUDY IN SAARC MEMBER STATES

L. Shrestha[1], K. K. Jha[2]

[1]Epidemiologist, SAARC TB and HIV/AIDS Centre, [2]Director, SAARC TB and HIV/AIDS Centre

Abstract

Objective: To assess the gender differences in TB suspects undergoing smear microscopy, TB case detection and treatment outcome under National TB Control Programmes of SAARC member countries.

Method: This is a cross sectional, record based retrospective study. Using a uniform format sex specific data were collected under the categories of TB case detection, TB suspects undergoing sputum microscopy and treatment outcomes of TB patients recorded during the last 2 quarters of 2004 (1 July – 31December 2004). For this purpose 5 TB diagnostic and treatment centres from each of seven member countries were randomly selected. Data sources were routinely maintained TB registers, TB laboratory registers and quarterly reports on case finding. The data were collected locally under the supervision of respective programme managers according to the guidelines prepared by the STC. All the collected data were processed and analyzed by STC using MS excel and Epi-Info soft ware- 6.

Results: Male/Female ratio of more than one was observed among the TB suspects undergoing sputum examination in all the countries except in Pakistan where it was less than one. Significantly higher sputum positivity among male TB suspects was also observed in India, Sri Lanka and Bangladesh where as in Nepal this sputum positivity was similar in both sexes. Overall regional sputum positivity was significantly higher in male TB suspects.

Male/Female ratio of more than one was observed in total (all types) TB case detection in all 7 countries with an exception in Pakistan. Males are more affected as new smear positive and smear negative PTB than female where as in new extra pulmonary TB category females are more affected than males.

Age and gender wise distribution of new smear positive cases revealed F/M ratios of less than one for all the age groups above 15 years, but more than one for the age group 0-14 years.

Successful outcome (cured & treatment completed) is around 86% and unsuccessful outcome is around 14% in both sexes. Regarding gender distribution of Cured and Treatment failure it is found to be similar in both sexes where as in relation to defaulter and died, males are more affected than female. However in case of transferred out, females are affected more than male.

Conclusion: The SAARC region being one of the most gender sensitive regions in the world, existing gender inequalities may reflect gender differences in TB epidemiology. The results of this study support to derive testable hypotheses such as; gender differences in susceptibility to TB infection and treatment outcomes. This reflects there might be presence of differential in health seeking behaviors and medical care at the health care units in all member states of SAARC. Further studies are needed to examine those hypotheses.

Key Words: Gender, disparity, suspects, positivity, sputum

Correspondence to:
Dr. Lochana Shrestha
Epidemiologist
SAARC TB and HIV/AIDS Centre
Thimi, Bhaktapur, Nepal
E-mail: saarctb@mos.com.np

Introduction

The impact of gender on health has been largely ignored and in TB research and control efforts, gender was not just missing, it was also considered unnecessary. In the last few years, however, as TB re-emerged onto the international and national public health agendas, inter-disciplinary studies and control efforts have begun to focus on the role of gender for this disease.

The magnitude of the global tuberculosis epidemic is enormous. About a third of the world's population is infected with *Mycobacterium tuberculosis.* In 1998, about three-quarters of a million women died of TB, and over three million contracted the disease, accounting for about 17 million disability adjusted life years (DALY). It is the greatest single infectious cause of death in women worldwide.[1] Literature on gender and TB is scanty: only a few succinct reviews on epidemiological and socio-cultural gender differentials and a report of a recent international workshop on the subject.[2,3,4] Worldwide, more men than women are diagnosed with TB. It is not clear to what extent these differences result from biological factors, socio-cultural contexts, and from under-recognition of TB among women due to poor access to care.

TB can be regarded as a symptom of poverty caused by the unequal distribution of resources globally. However, poverty within a society is not distributed equally among its social classes, and between the two sexes. Estimates show that 70% of the world's poor are women.[5] Poverty and gender are implicated in a woman's vulnerability to TB. As described previously the low status accorded to women in most male dominated South Asian countries, their limited decision making powers, restricted mobility and poor access to health care resources make them particularly vulnerable to TB and reduce opportunities in accessing basic and available health care. On the other hand men being the breadwinners of the families, run a high risk of exposure to infectious diseases such as TB and predisposing factors like smoking, alcohol, drug abuse etc as they are constantly on the move within their societies.

Higher tuberculosis notification rates in men may partly reflect epidemiological differences in exposure, risk of infection, and progression from infection to disease. Some studies indicate that women may have higher rates of progression from infection to disease and a higher case fatality in their early reproductive ages.[5]

Background

TB is a global problem and the problem is disproportionately higher in SAARC region[6]. With 22% of the world's population, SAARC region accounts for more than 27.9% global TB burden.[6] Some SAARC countries, India, Bangladesh, Pakistan and Afghanistan have been listed among the 22 high burden countries.[7]

2.1 million smear positive cases notified by DOTS programmes in 2004 represent 53% of the entire estimated incidence[8]. The case detection rate of sputum smear positive under DOTS increased to reach 64% in 2004. In 2005, of the estimated 3 million new cases a total of 1939356 cases were reported in the SEA region.[9] There is growing recognition that the increasing global burden of TB is related to HIV/AIDS and thus now the threat is from TB/HIV co-infection. One possible reason for this overall low case detection rate may be under-reporting of female cases.

Overall case notification rates for TB globally and also in SAARC region are consciously showing higher rates for males.[7] When comparing the male to female ratio in the different age groups twice as many girls than boys were detected in the age group 0-14 years, whereas almost four times as many men as women were detected in the oldest age groups.[9]

Males and females are almost equally distributed within the populations of SAARC member Countries[10]. With such population distribution between sexes, the low detection of female TB cases remains a troubling public health issue demanding urgently focused study. Accordingly several studies conducted focused on different aspect of gender differentials on TB epidemiology. The study with the view to compare infection and disease rates, women of reproductive age have shown high progression rate to disease from infection compared with the men of same age group[10]. Results from a study in Nepal comparing active and passive case finding methods showed higher detection of female TB cases by active case detection method in comparison to passive case detection method (46% Vs 28%)[10]. Another study in Nepal found that women had a longer total delay

before diagnosis of Tuberculosis than men.[11] These facts pave the way to the assumption that female TB cases are under detected & under reported.

Gender differences occur not only at access to health care, but also at diagnosis (smear microscopy) and treatment outcome levels too. A study in Bangladesh on sex differences in diagnosis and treatment outcome revealed low female to male ratios (less than 1) in tuberculosis suspects undergoing smear microscopy, and suspects diagnosed with positive smears which were 0.51 and 0.35 respectively.[12]

To see the gender differences among TB patients in National TB Control Programmes within SAARC Member States, STC conducted a study during 2001[13] in which overall female/male ratio of less than 1 was observed in case of TB suspects undergoing sputum examination, sputum positivity and in total TB case detection.

A community based study[14] conducted by STC in Kathmandu found more female TB suspects than males (male: female = 62:81) in the community. On the other hand an institutional based study done by STC in Dhaka revealed a male: female ration 1:08 among TB suspects identified from attending chest symptomatics[15].

Identification of gender differences in TB epidemiology and other aspects would provide a sound basis to study gender inequalities occurring at the various levels of effective TB care. The differential impact of gender issues on the management of tuberculosis and the potential for gender analysis to inform effective interventions and policies to better control Tuberculosis is now identified.[2]

Since the introduction of DOTS in Member States, 10-12 years have been passed and remarkable progress has been made in TB control. By this time different sectors of the society have been involved in the programme and awareness among general population about TB has been high. In this situation it is imperative to assess the magnitude of gender differences in TB epidemiology at various levels of effective TB care.

Hence this particular study is carried out at the regional level which would allow to assess gender differences in TB epidemiology in the whole SAARC region as well as to compare the differences between member countries. Furthermore, this retrospective descriptive epidemiological analysis of available TB data within SAARC regional countries represents the attempts to generate basic estimates by gender for the whole region. Such estimates are mandatory as a foundation for generating future testable hypotheses, and remain vital for effective TB care.

Objectives

- To assess the gender differences in TB suspects undergoing smear microscopy and smear positivity in selected areas of SAARC Member States.
- To assess the gender differences in TB case detection and treatment outcome in those selected areas of SAARC Member States.

Methods

The study design was a cross sectional institutional based with review of recorded TB data from registers used in TB Programme. The study population included reported cases of new Tuberculosis patients and Tuberculosis symptomatics (TB suspects) from randomly selected five TB treatment centers (which have diagnostic facilities) from each SAARC country except in Maldives where the data is provided for whole country in the period of 1 July 2004 to 31 December 2004*(last two quarters of 2004). Data sources was the routinely maintained TB register, TB laboratory register and quarterly report on case finding.

Sex specific data was collected for TB symptomatics undergoing sputum examination, case detection under all types of new TB cases (new smear positive, new smear negative and new extra pulmonary), along with their treatment outcomes. Age wise sex disaggregated data was collected only for new smear positive cases. Last 6 months of the year 2004 have been chosen as the review period for having completeness of the available data within that period and all cases within this period was included (providing completeness of case data) in analysis.

Data collecting formats prepared by STC on the basis of the WHO approved quarterly TB data collecting

formats were used for data collection. The data was collected locally under the supervision of respective TB programme manager according to the guidelines prepared by the STC. All the collected data was processed and analyzed by STC using MS excel and Epi-Info software. The Chi square values were calculated using Epi Info. 6.

Results

Gender Differences in TB Suspects (undergoing Sp. Exam.) and Sputum positivity

In this institutional record based study 27293 TB suspects underwent sputum examination in selected 30 centres, about 5 centres in each member states and among them 15913 (58%) were males and 11380 (41%) were females with over all male/female ratio 1:0.7. M/F ratios in TB suspects undergoing sputum examination varies from 1/0.5 – 1/1.3. In all the countries except Pakistan male/female ratio in TB suspects undergoing sputum examination was more than one. In Pakistan this ratio was 1:1.3 (see table 1).

In Pakistan number of female TB suspects were significantly higher than that of the male suspects (p<0.001) while in other countries female TB suspects were significantly lower (p<0.001).

Table 1 TB Suspects (undergoing sputum examination) and Gender

Country	TB suspects undergoing sputum examination			
	Male	Female	Total	M:F ratio
Bangladesh	1648	989	2637	1:0.6
Bhutan	934	793	1727	1:0.8
India	3023	1759	4782	1:0.5
Maldives	562	411	973	1:0.7
Nepal	731	477	1208	1:0.6
Pakistan	1610	2088	3698	1:1.3
Sri Lanka	7405	4863	12268	1:0.6
Total	**15913**	**11380**	**27293**	**1:0.7**

Table 2 Sputum Positivity among TB Suspects by Gender

Country	Number of TB suspect under going sputum examination		TS showing positive result No (%)		Chi-square value	P-Value
	Male	Female	Male %	Female %		
Bangladesh	1648	989	238(14.4)	103(10.2)	8.90	0.002
Bhutan	934	793	74(7.9)	46(5.8)	2.90	0.08
India	3023	1759	508(16.8)	186(10.5)	34.79	0.00
Maldives	562	411	22(3.9)	9(2.1)	2.29	0.13
Nepal	731	477	108(14.4)	70(14.6)	0.00	0.92
Pakistan	1610	2088	254(15.7)	309(14.8)	0.67	0.41
Sri Lanka	7405	4863	551(7.4)	198(4.07)	58.13	0.00
Total	**15913**	**11380**	**1755(11.02)**	**921(8.09)**	**69.66**	**0.00**

Table 2 showed among TB suspects 1755 (11.02%) male and 921(8.09%) female were found to be sputum positive for AFB which is significant (p<0.001). It can be said that sputum positivity is significantly higher among male TB suspects than in female TB suspects in Bangladesh (p<0.01), India (p<0.001) and Sri Lanka (p<0.001). In percentage sputum positivity among female TB suspects is lower than in male TB suspects in all countries except Nepal where it was found to be similar in male and female.

Table 3 Category wise New TB cases by Gender

Country	New Smear + PTB		New smear - PTB		New Extra Pulmonary TB		All cases		
	Male	Female	Male	Female	Male	Female	Male	Female	F/M Ratio
Bangladesh	260	126	60	20	22	18	342	164	0.5
Bhutan	48	21	22	18	37	56	107	95	0.8
India	380	149	150	99	117	94	647	342	0.5
Maldives	22	9	5	2	8	11	35	22	0.6
Nepal	114	61	100	64	46	51	260	176	0.7
Pakistan	180	224	104	128	121	119	405	471	1.1
Sri Lanka	727	263	259	144	183	190	1169	597	0.5
Total	**1731**	**853**	**700**	**475**	**534**	**539**	**2965**	**1867**	**0.6**

Table 3 described the category wise New TB cases by gender in seven member countries. Among total (all types) new TB cases, 2965 (61%) were males and 1867 (39%) were females with a female/male ratio of 0.6.Female/male ratios in total (all types) TB cases at country level varied from 0.5 – 1.1, the lowest ratio (0.5) being from Bangladesh, India and Sri Lanka. The other countries showing F/M ratio less than one are Nepal and Bhutan. The highest F/M ratio (1.1) was from Pakistan. In relation to total all new cases, In Pakistan the female cases are higher than male cases while in other countries (Bangladesh, Bhutan Sri Lanka, India, Maldives and Nepal) the female cases are lower than male cases.

During the period total 2584 new smear positive cases were reported from 7 countries and it accounted for 54% of the total number of new cases. Number of new smear negative cases reported from 7 countries were 1175 and new extra pulmonary cases 1073 which accounted for 24% and 22% of the total number of cases respectively. In comparing the male and female distribution among different categories of New TB cases, among new extra pulmonary TB cases female cases are found to be more than male in four countries(Bhutan, Sri Lanka, Maldives and Nepal) and almost similar in other 3 countries (Bangladesh, India and Nepal) whereas in other categories males are more than female.

Among the total (2676) male and female smear positive TB suspects, 2584 (96%) were New smear positive PTB (67% male and 33% female).

Table 4 New Smear Positive cases by Age and Gender, in SAARC Countries

Age group	Bangladesh		Bhutan		India		Maldives		Nepal		Pakistan		Sri Lanka	
(years)	M	F	M	F	M	F	M	F	M	F	M	F	M	F
0-14	2	3	0	1	5	5	0	0	2	3	6	30	1	2
15-24	39	23	16	9	78	38	7	3	26	21	53	55	93	53
25-34	38	31	11	4	78	39	4	1	16	12	43	59	96	54
35-44	44	29	4	3	83	24	2	2	20	10	27	30	161	45
45-54	50	15	6	1	65	17	4	0	24	4	15	20	197	47
55-64	46	14	3	2	44	18	3	1	16	7	18	18	95	27
65+	41	12	8	1	27	8	2	2	12	4	18	12	85	35
Total	**260**	**127**	**48**	**21**	**380**	**149**	**22**	**9**	**116**	**61**	**180**	**224**	**728**	**263**

The data on New smear positive pulmonary TB cases (Table 4) revealed that in all the SAARC countries number of male reported cases are more than that of female cases in the over 15 years age group except Pakistan where in all age groups except above 65 years females are more than male.

Table 5 New Smear Positive cases by Age and Gender, SAARC Region

Age group (years)	New Smear + cases		Chi-square Value	P- Value
	Male	Female		
0-14	16	44	45.20	0.00
15-24	312	202	11.52	0.00
25-34	286	200	17.90	0.00
35-44	341	143	3.21	0.07
45-54	361	104	28.90	0.00
55-64	225	87	4.20	0.04
65+	1293	109	1.48	0.22
Total	**1734**	**854**		

After adding all country data and performing chi-square test (Table 5) it is found that in all the age groups of total new smear positive TB cases the number of male patients were significantly higher ($p < 0.001$) than that of female patients in all age groups except in age groups of 55-64 and 65+ years. And in fewer than 15 age group females patients were significantly higher than the male patients. Age wise distribution of New smear positive cases shows that the majority of cases are spread between the ages from 15 to 54 (economically productive age group) in both sex groups in all member countries (Figure 1a). Fig 1b showed that majority of cases are within 15-54 years group in all member countries except in Pakistan and Sri Lanka where the distribution is same in all age groups.

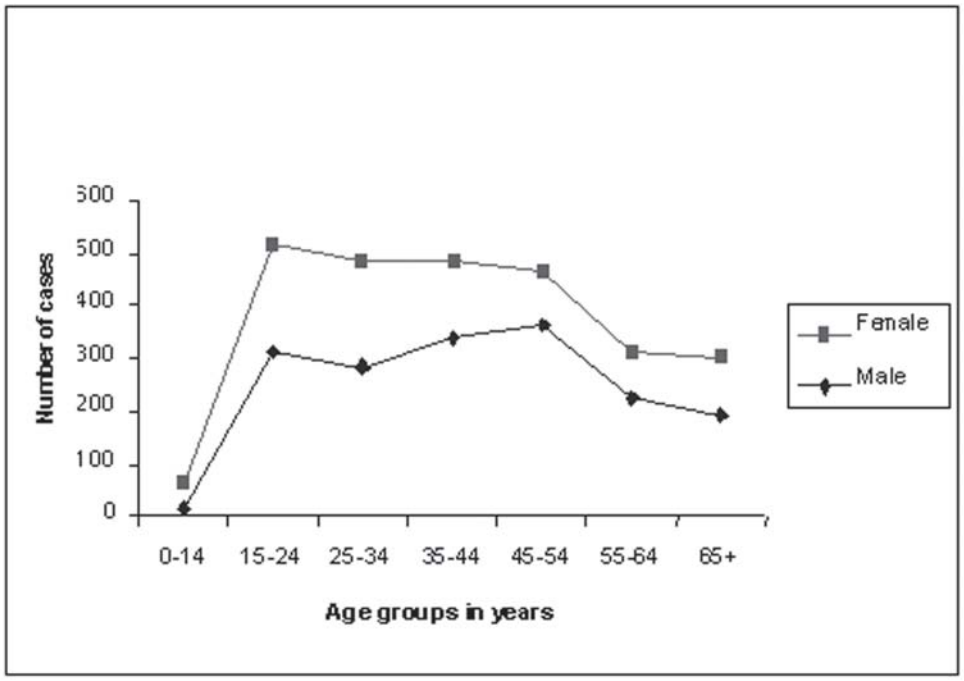

Figure 1a: Age & Gender Distribution of New Smear Positive Cases, SAARC region

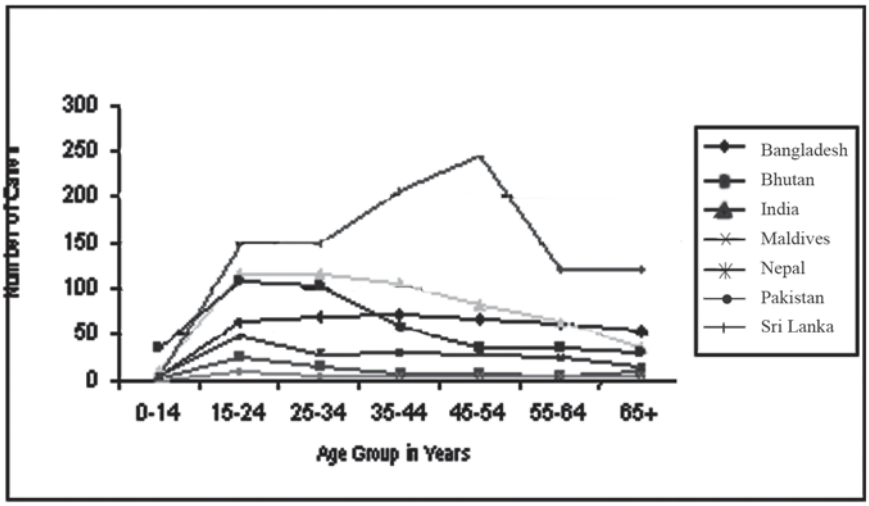

Figure 1b: New Sputum Smear +ve. Cases by Age in SAARC Member States

Combining both sexes, 75% of cases from the total new smear positive cases belong to age group (15-54). Country wise gender disaggregated data showed that in Bangladesh, Bhutan and Nepal proportion of female adult (age 15-54) TB cases are higher than that of male adult TB cases out of total TB cases. This gender difference in proportion of adult TB cases was significantly higher ($p< 0.05$) in Bangladesh and Nepal. In other countries this proportion in both sex groups is found to be similar as well as in regional level. (figure 2).

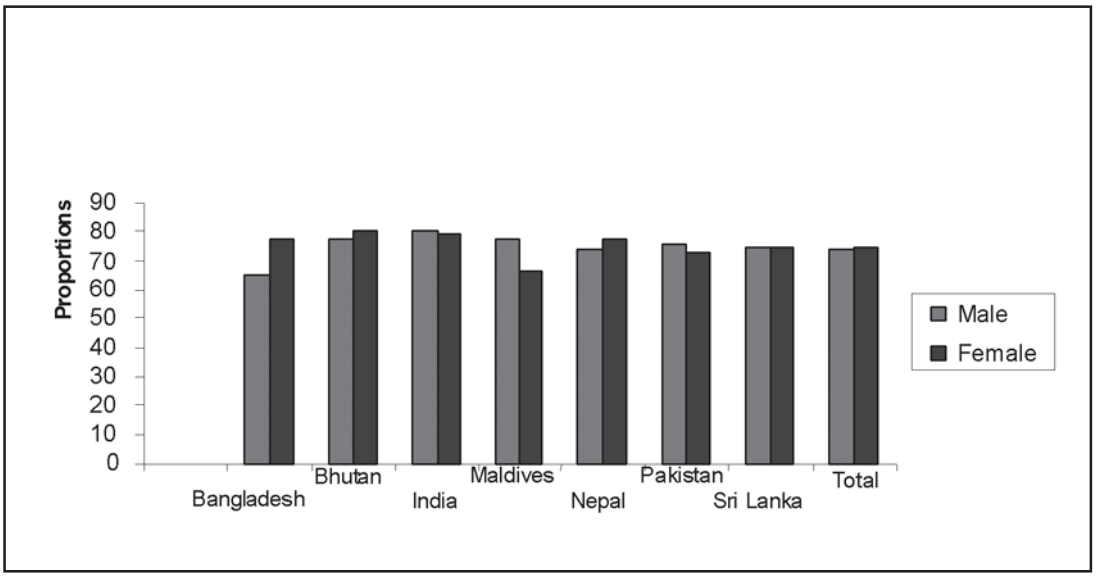

Figure 2: Proportions of Adults in 15-54 Year Age Group out of Total New Smear Positive Cases by gender

Treatment Outcomes by Gender

In comparing the treatment outcomes in terms of treatment success (Cured & Treatment completed) in majority of countries (4 countries; Bhutan, Maldives and Pakistan) there is no significant gender difference. A significant gender difference (p value<0.05) is seen in other 3 countries (Bangladesh, India, Nepal and Sri Lanka) where treatment success rates are significantly higher among male TB patients. (Table 6)

Table 6 Treatment Success (cured + treatment completed) among New Smear positive cases by Gender

Country	New Smear Positive Registered		Treatment Success		Chi-square value	P-Value
	Male	Female	Male	Female		
Bangladesh	260	136	243	110	4.12	0.04
Bhutan	46	37	36	34	2.88	0.08
India	379	149	333	135	0.8	0.37
Maldives	22	9	21	8	0.41	0.49
Nepal	114	71	101	49	19	0.00
Pakistan	169	224	139	173	1.48	0.22
Sri Lanka	731	260	606	248	29.6	0
Total	**1721**	**886**	**1479**	**757**	**0.12**	**0.73**

Default rate during TB treatment found significantly higher among male TB patients than those in female TB patients in case of Pakistan and Sri Lanka only. Also in overall regional total New smear positive cases default rate among males are significantly higher. (Table 7)

Table 7 Default among New Smear positive cases by Gender

Country	New Smear Positive Registered		Default Cases		Chi-square value	P-Value
	Male	Female	Male	Female		
Bangladesh	260	136	5	4	0.42	0.51
Bhutan	46	37	6	1	2.80	0.09
India	379	149	18	5	0.50	0.48
Maldives	22	9	0	0	nv	
Nepal	114	71	1	3	2.32	0.12
Pakistan	169	224	26	20	3.80	0.04
Sri Lanka	731	260	64	5	13.82	0.00
Total	**1721**	**886**	**120**	**38**	**7.4**	**0.006**

Regarding **Death** during TB treatment, no significant difference is seen between males and females in all countries except in Sri Lanka where the difference is significant between male and female ($p < .01$). (Table 8)

Table 8 Death among new smear positive cases by gender

Country	New Smear Positive Registered		Number Died		Chi-square value	P-Value
	Male	Female	Male	Female		
Bangladesh	260	136	12	7	0.06	0.18
Bhutan	46	37	2	0	1.65	0.19
India	379	149	23	7	0.37	0.54
Maldives	22	9	1	1	0.46	0.49
Nepal	114	71	5	2	0.30	0.58
Pakistan	169	224	4	12	2.21	0.13
Sri Lanka	731	260	44	6	5.51	0.01
Total	**1721**	**886**	**91**	**35**	**1.54**	**0.21**

Treatment failure rate during TB treatment found significantly higher among male TB patients than those in female TB patients in case of Pakistan while in Maldives significantly higher among female TB patients than those in male TB patients. In other countries and in overall regional level in this aspect there is no significant difference between males and females (Table 9).

Table 9 Treatment Failure among New Smear positive cases by Gender

Country	New Smear Positive Registered		Treatment failure		Chi-square value	P-Value
	Male	Female	Male	Female		
Bangladesh	260	136	8	2	0.94	0.33
Bhutan	46	37	1	3	1.57	0.20
India	379	149	0	1	2.55	0.11
Maldives	22	9	1	3	4.70	0.02
Nepal	114	71	2	3	1.02	0.31
Pakistan	169	224	9	0	12.21	0.00
Sri Lanka	731	260	0	0	nv	
Total	**1721**	**886**	**21**	**12**	**0.08**	**0.77**

In comparing the different treatment outcomes in total new smear positive cases, successful outcome (cured & treatment completed) is around 86% and unsuccessful outcome is around 14% in both sexes. (Table 10)

Regarding gender distribution of Cured and Treatment failure it is found to be similar in both sexes where as in relation to defaulter and died males are more affected than females. However in case of transferred out, females are more than male.

Gender difference in relation to defaulter and transferred out is significant where as in other outcomes there is no significant difference. (Table 10)

Table 10 Treatment Outcomes of New Smear Positive (NSP) Cases

Category of treatment outcome	New Smear Positive Cases		Chi-square value	P-Value
	Male %	Female %		
Cured	1414 (82%)	719 (81%)	0.4	0.52
Treatment completed	65 (3.7%)	38 (4.2%)	0.4	0.52
Treatment Failure	21 (1.2%)	12 (1.3%)	0.08	0.77
Defaulted	114 (6.6%)	38 (3.8%)	5.8	0.01
Died	91 (5.2%)	35 (3.9%)	2.27	0.13
Transferred out	22 (1.2%)	33 (3.7%)	16.95	0.00
Successful Outcome	1479 (85%)	757 (85%)	0.12	0.73
Unsuccessful Outcome	248 (14.4%)	118 (13.3%)	0.58	0.44
Total NSP	**1721**	**886**		

Discussion

Objective of this study was to find out gender differences in TB epidemiology with regard to sex ratios of TB suspects undergoing smear microscopy and smear positivity, case detection and treatment outcome by collecting data from selected centers in SAARC countries.

According to the results of this study, there is low female case detection, low number of female TB suspects undergoing sputum examination, and low sputum positivity among females TB suspects in overall 7 countries (exception in Pakistan with reversal of ratios). It is difficult to make a definitive

statement for Pakistan's reversal of sex ratios as the number of TB cases observed in this study turned out to be low. Similar finding was found in the previous study done by STC in all Member States during 2001[13]. Also the study done by A.N. Martinez *et al*[16] in San Francisco showed the significantly higher case detection among male than in female. Similarly study done in Western Cape region of South Africa by Austin et al[17] revealed outnumbered among male TB suspects. These findings suggest the possibility that cases of tuberculosis among women are being under reported in developing regions. This hypothesis is supported by a study in Eastern Nepal that utilized active and passive case finding methods[11].

Age-wise distribution of new smear positive cases showed M/F ratio of more than 1 for all the age groups above 15. However in 0-14 age group M/F ratio was less than 1. This age wise distribution in new smear positive cases is consistent with the TB data from SAARC countries, Tuberculosis Control in the South East Asia Region 2006, WHO/IUALTD reports on Global Tuberculosis control 2005 and 2006. This deviation of sex ratios in case detection in 0-14 age group from other age groups cannot be explained in precision and it demands further studies. However, epidemiological surveys have shown the prevalence rates as well as tuberculin positivity among women to be consistently lower after the age of 15. Some of this difference is attenuated because women of reproductive age are at greater risk of progressing from infection to disease than are men of the same age[18].

With regard to the treatment outcomes (treatment success, default, treatment failure, death and transferred out) no significant difference was observed between sexes in a majority of countries. Although there is a significant difference between males and females in defaulter rate and transferred out rate. Defaulter rate is significantly higher in male and transferred out rate is significantly higher in female. Proportion of successful outcome and treatment failure is similar in both sexes. In treatment completion female proportion is higher than male whereas in defaulter male proportions are higher. In contrast the study done by J Date et el[19] in Japan presented the higher proportions of successful outcomes among female than in male.

This finding may signify that females have better treatment compliance once they are diagnosed. While women may have to negotiate more barriers in seeking treatment for TB, they tend to be more compliant than men in taking it. The findings that males are less likely to complete the treatment than female may be linked to the gender roles of the tribal society.

Conclusion

SAARC region is one of the most gender sensitive regions in the world with females confronting many gender-based inequalities. Such inequalities may impose an impact on Female's health in terms of their poor health seeking behavior and obtaining health care services.

In this study females are significantly lower than male in relation to TB case detection, TB suspects and sputum positivity. However treatment outcome is found to better in female than in male. The results of this study support to derive testable hypotheses such as; gender differences in susceptibility to TB infection and treatment outcomes. This reflects there might be presence of gender differential in health seeking behaviors and medical care at the health care units in all member states of SAARC. Several factors have clearly different effects on the care seeking and treatment behavior for TB among men and women. Further studies are needed to examine those hypotheses. Future studies should include qualitative analyses that probe the underlying reasons for these differences and enable the design of effective interventions. National Tuberculosis programmes must assess possible sex differences that exist in their countries.

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SOCIO-DEMOGRAPHIC PROFILE AND OUTCOMES OF THE ADMITTED AIDS PATIENTS IN BPKIHS, NEPAL

Mehta RS[1]***, Shrestha R***[2]***,***

[1]*Asst. Professor, Medical-Surgical Nursing Department2*
[2]*Asst. Professor, Dept. of Medicine, In-charge, Infectious Disease unit*
B.P. Koirala Institute of Health Sciences, Dharan, Nepal

Abstract

Introduction: In the world More than 40 million people are living with HIV/AIDS, 2.3 million are under 15 yrs, 14000 new infections each day, 3.1 million deaths from AIDS. In south East Asia 6.3 million people living with HIV/aids in 2005.

Objectives: To find out the socio-demographic profile and outcomes of the admitted AIDS patients in B.P. Koirala Institute of Health Sciences.

Method: This retrospective descriptive study was conducted at B.P. Koirala Institute of Health Sciences (BPKIHS) among the admitted AIDS cases during the period of 1-9-2003 to 30- 8-2006. It was found that majority of the subjects (83.4%) were at age group of 20-40 years, Male (89.6%), and from Sunsari district (47.9%). Half of the subjects were improved after treatment and then discharged.

Conclusion: As the number of AIDS cases are increasing rapidly in eastern Nepal and BPKIHS is a centre for treatment of AIDS cases, it is essential to conduct awareness activities regarding prevention of disease and advocacy about available facilities of BPKIHS.

Key words: AIDS, Socio-demographic profile, BPKIHS

Introduction

In Nepal the estimated number of People Living with HIV/AIDS (PLWHA) at the end of 2005 is 61,000, HIV prevalence was 0.5, with an estimated number of AIDS cases 7,800 & number of child (0-18) orphaned by HIV/AIDS was 18000 & receiving Anti Retroviral Treatment (ART) till December 2005 was 210. HIV infection has taken root in South Asia and poses a threat to development and poverty alleviation efforts in the region. HIV infection is fueled by risk behavior, extensive commercial sex, low condom use and access, injecting drug use, population movements (cross-border/rural-urban migration) and trafficking.[1]

Correspondence to:
Dr. R. S. Mehta
Asst. Prof., Medical-Surgical Nursing Department
B.P. K. H. S., Dharan, Nepal
Email:ramsharanmehta@yahoo.com

Social and economic vulnerabilities, including poverty and illiteracy, highlight the need to act effectively and aggressively to reduce it's spread. In South Asia while overall HIV prevalence rates remain relatively low, the region's large populations mean that a rise of a mere 0.1% in the prevalence rate in India, for example, would increase the national total adults living with HIV by about half a million persons.[2]

The current situation of HIV in Nepal is different from when the first case was diagnosed in 1988. There are gaps and challenges to be addressed in the fight against HIV and AIDS. Nepal is low prevalence country for HIV and AIDS. However, some of the groups show evidence of a concentrated HIV epidemic e.g. sex workers (19.5%), migrant population (4-10 %), and intravenous drug users (IVDU's) both in rural and urban areas (68 %). Since 1988 when the first case was diagnosed MoHP/DoHS and different stakeholders came forward to address HIV and AIDS issues.[1]

A significant percentage (60%), of HIV positive patients belongs to lower socio-economic class and many of them were mobile workers and contracted their illness while working in Indian metropolis in the past reported by Aich[5] in their study.

Study conducted by Agrwal[6] reported that there was a significant difference in the domain concerning social relationship between the HIV positive individuals with the controls.

Study conducted by Parakh[7] at BPKIHS among the health professionals showed that health professionals had a hesitation in treating patients with HIV/AIDS, tempered by concerns regarding provision of such care.

Study conducted by Asrath[10] among migrant workers in eastern Nepal found that, majority of migrant workers (94.9%) had heard of HIV/AIDS, but only few know the symptoms of AIDS. Most of them were aware that the use of condom prevents the spread of HIV/AIDS but 25% of them do not use, while having pre/extra marital sex. About 11.9 % workers were going to sex workers at a regular intervals and no one was using condoms.

HIV/AIDS is emerging as a major threat in the socio-economic and health sectors of Nepal. Their multiple effects have so far been minimal in the country, but their potential impact is immense.

Methods

This is a retrospective descriptive study conducted at BPKIHS among the admitted AIDS clients. The available Case-sheets of the diagnosed AIDS cases admitted in between 1st September 2003 to 30th August 2006 constituted the population of the study. The total 48 AIDS cases were included in the study. Using total enumerative sampling technique all the case notes were collected from the medical record section using coded numbers (B 24, ICD–10) of files from September 1, 2003 to August 30, 2006 i.e. Bhadra 15, 2060 to Bhadra 14, 2063 after taking written permission from the hospital director. The files not available and incomplete were excluded. Using standard semi structured Performa the data/information were collected.

Anonymity of the subjects was maintained. The information obtained was kept confidential and used only for this study. The collected data was entered in SPSS-10.5 version software package and analyzed. The findings are presented in tables and graphs. Using Percentage, Mean and SD the demographic findings and outcomes were described.

Results

The number of AIDS cases admitted in BPKIHS is increasing day by day i.e. 10, 12 & 16 in the years 2004 (2061BS), 2005 (2062 BS), and 2006 (2063 BS) respectively as per the record but actual number is much more because the files are coded on the basis of written diagnosis on the admission discharge sheet, which was usually accurately filled and only the admitted diagnosis is mentioned. Now, BPKIHS is a centre for treatment of AIDS cases of Eastern Nepal, where the facilities of HIV testing, Anti Retroviral Treatment (ART), PMTCT, VCT, and regular OPD services are available.

Table 1 Socio-Demographic Profile and Outcomes of the Admitted AIDS Patients in BPKIHS (N=48)

SN	Item/Particular	Percentage (%)
1	**Age group of the subjects:**	
	< 20 years	8.3
	20-30 years	48.0
	30-40 years	35.4
	>40 years	8.3
	Mean	**29.26**
	SD	**9.4**
	Range	**2-50 Years**
2	**Gender:**	
	Male	89.6
	Female	10.4
3	**Caste of the subjects:**	
	Brahmin/ Chetri	29.2
	Mangolian	50.0
	Newar	2.1
	Teri Origin	18.8
4	**District Wise distribution of the subjects:**	
	Sunsari	47.9
	Morang	18.8
	Jhapa	14.6
	Sirha	4.2
	Others: (Mahotari, Dhankuta,	
	Dhanusa, Ilam, Taplagunj, Udapur)	10

15	**Duration of hospitalization:**	
	< 5 days	41.7
	5-10 days	29.1
	10-15 days	20.9
	> 15 days	8.3
	Mean	**7.98**
	SD	**5.32**
	Range	**1-28 days**
6	**Department wise distribution of the subjects:**	
	Medicine	89.6
	Pediatric	6.3
	Surgical	4.2
7	**Outcome of the clients:**	
	Improved & discharged	50.0
	Unchanged & discharged	22.9
	Expired	14.6
	LAMA	8.3
	Discharge on Request	2.0
	Absconded	2.0

Demographic Profile of the subjects

Table one showed that majority of the clients were of the age group 20-40 years i.e. 83.4%, which is of similar pattern with national as well as international trends. Majority of clients were male (89.6%). Majority of the clients were Mangolian (50%). Similar demographic data were reported by Agrwal.[6]

Most of the clients were from sunsari (47.9%), Morang (18.8%), and Jhapa (14.6%), as BPKIHS is situated in Dharan which is easy for arrival by the population of these three districts. There are three municipalities in Sunsari, one in Morang, and two in Jhapa. Most of the clients are admitted under medicine department (89.6%) being adult patients.

Outcomes of the clients

Half of the clients were improved with the symptoms and discharged, where as 22.9% were unchanged. The disease is not curable but manageable; hence life long treatment is required along with management of opportunistic, infections if occurred. The symptoms will persist and client will die if HIV infection is not detected in early stage and not started ART on time, when required.

Discussion

The report on the pattern of demographic and clinical profiles of HIV positive persons in Nepal are scarce.[5] HIV/AIDS is rapidly spreading in countries of Asia including Nepal. Reporting may be low due to social stigma and ignorance of diseases among female. It could cause major socio-economic impact in the country. It obviously has many health implications.[9] HIV/AIDS is a growing public health problem with complex social and behavioral issues related to protection, prevention of transmission and care for nursing and midwifery personnel caring for people living with HIV/AIDS.[8]

Conclusions

HIV/AIDS is no longer only a health issue; it is also a development issue. To tackle the epidemic, along to prevention and control of HIV infection among vulnerable and risk groups but a multi-sectoral approach is needed to address the lack of access by risk groups to health care education and recognition of the populations at risk. People living with HIV and AIDS should be brought to the forefront in the fight against HIV/AIDS. Family members, local communities, civil society organizations, donors, and government all have their own important role to play. Increasing trend of the disease certainly has given pressure to focus on the use of comprehensive targeted intervention programs in risk group sub-populations. AIDS is a chronic manageable disease, which is common among age groups of 20-40 years of their productive life. If proper treatment and care is provided the life of the clients can be prolonged with comfort. Keeping the emerging trends in mind it's mandatory to provide pubic awareness regarding the nature of disease, prevention of further spread and advocacy about availability of services and their utilization among the public like: HIV testing, screening OPD, VCT, PMTCT, ART, Management of opportunistic infection, CD-4 count services and other services of HIV/AIDS available at BPKIHS along with elimination of social stigma so that clients can approach easily at hospital and will be benefited with available facilities.

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BARRIERS IN SEEKING HEALTH CARE AMONG TB SUSPECTS (TS) AN INSTITUTION-BASED CROSS SECTIONAL STUDY IN DHAKA BANGLADESH

Jha K K,[1] Begum V,[2] Islam Md N,[3] Faruq A K M M R,[4] Rahman Md. M,[5] Piryani R M[6]

[1] Director, SAARC TB and HIV/AIDS Centre
[2]Programme Manager, NTP, Bangladesh
[3]Superintendent, TB Control & Training Institute, Chankharpool, Dhaka
[4]Officer-in- Charge, National TB Control Project, Shyamoli, Dhaka
[5]Ex-epidemiologist,
[6]Ex-Deputy Director, SAARC TB and HIV/AIDS Centre, Nepal

Abstract

Setting: Two TB diagnostic centres- TB Control & Training Institute, Chankharpool and National TB Control Project, Shyamoli in Dhaka city were the study places.

Objectives: To assess the pattern of health seeking behaviour and to explore the barriers in seeking health care among the TB suspects with gender differentials.

Design and Methods: An institution-based, cross sectional study was conducted from July to September 2005 among 998 identified TB suspects of both sexes and of ages 15 years or more. Information on socio-demographic characteristics, presenting symptoms/complaints, health seeking behaviour and barriers in seeking health care were collected by using pre-tested semi-structured questionnaires.

Results: Overall male: female ratio was 1:08. More than 52% of the TB suspects were below 30 years of age. Higher number of females were found in the age group of 15-19 years and beyond that, males were more. Overall mean age was significantly higher in male TB suspects than that in the female TB suspects (p<001). About 68% of the TB suspects were from urban area and no sex difference was found regarding their place of residences, (p >0.05). Mostly they were from low socio-economic status. Along with cough other complaints were chest pain (87%), fever (82%), night sweat (62%), loss of appetite (86%), loss of weight (89%) and blood in sputum (33%). Compared to males higher number of females complained of fever, chest pain and loss of appetite (p <0.05 in each case). Durations of symptoms showed no significant sex difference except night sweat by which female suffered for longer duration (p=0.044). About 17% of the TB suspects did not seek any advice for their symptoms. In this regard there was no significant sex difference. The most common cause for not seeking health care was lack of awareness or ignorance (52%). Others causes were want of money (32%) and lack of time (15%). Among those who sought advice for their symptoms, 42% visited paraprofessionals or irrelevant sources and another 38% visited either qualified private practitioners or private hospitals. Only 16.5% visited government hospitals/health posts. No significant gender difference was found in this regard. Significantly more males had to loose wages and more females had to take an accompanying person for visiting the center. About 7.5% of the TB suspects faced some form of social stigmatization.

Conclusions: A substantial proportion of the TB suspects (TS) in this study did not seek health care due to lack of awareness or ignorance. Among those who sought advice for their symptoms, most of them visited paraprofessionals or private sectors. Some of the TB suspects faced social stigmatization problem. Strengthening of awareness programmes for paraprofessionals and expansion of public private partnership are vital to achieve the target of TB case detection.

Key Words: TB suspects; gender differences; barriers; health seeking

Correspondence to:
Dr. Kashi Kant Jha
Director,
SAARC TB and HIV/AIDS Centre
E-mail: saarctb@mos.com.np

Introduction

Tuberculosis causes an enormous burden of morbidity and mortality around the world. Nearly one-third of the world's population is infected with *Mycobacterium tuberculosis bacillus* and world wide more than 15 million people are suffering from active TB disease.[1,2,3] In 2003, globally there were 8.8 million estimated new TB cases, of which 3.9 million were smear- positive (infectious type).[3,4] Tuberculosis is the second leading cause of death among infectious diseases worldwide. Approximately 1.8 million deaths occur each year due to this disease.[1, 5]

SAARC Region bears disproportionately higher burden of tuberculosis problem. Almost half of the adult population of this region is infected with *Mycobacterium tuberculosis bacillus.* In the year 2003 the estimated new TB cases were 2.5 million (27.3% of the global) from this region where 22% of the global population resides.[4]

National Tuberculosis Programmes in this region has been operational since the early 1960's but has not been effective in terms of case detection or treatment outcome. Consequently DOTS strategy was initiated in 1993 and by 1996 all the SAARC member countries adopted this strategy. By end of 2003 SAARC Region covered nearly 71% of its total population. Treatment outcome was found satisfactory, with a success rate of 86% (regionally) but case detection was low (47% regionally). [4]

Reports of TB cases suggest, virtually in all countries, fewer female than male TB cases are notified.[6] Community based epidemiological studies have established that males have a higher prevalence of TB infection and a higher rate of progression from infection to active disease than females. [6,7] Yet there are concerns that females suffering from TB are underreported due to various socio-cultural factors e.g. reduced access to health care services, under-reporting of respiratory morbidity and greater stigmatization. [6]

Moreover, profound gender differentials existing in SAARC member countries may create barriers for women in seeking health care leading to under reporting of female TB cases in this region.[8]

Findings from a cross sectional community based study conducted in Kathmandu by STC suggest that majority of the TB suspects in the community though suffering from respiratory symptoms for a considerable period, are not seeking health care due to lack of awareness and ignorance.[9]

On same way this institution based study was framed to conduct in Bangladesh to identify barriers in seeking health care in TB Control Programme targeting people of diverse areas.

Objectives

- To assess the pattern of health seeking behavior among the TB suspects
- To explore the barriers in seeking health care among the TB suspects.
- To find out gender differences in health seeking behavior and in the barriers in seeking health care

Methodology

Type/design of study:
The study was Institution based, cross sectional study.

Study place, population and sample size:
Two TB diagnostic centres - TB Control & Training Institute, Chankharpool and National TB Control Project (NTCP), Shyamoli in Dhaka city were selected purposively for the study. Identified TB suspects referred for sputum microscopy by the attending physician(s) were the study population. TB suspects of both sexes and of age 15 years or more were included in this study after getting their informed consent.

Sample size and sampling technique:
A total of 998 TB suspects were included in this study. Consecutive sampling technique was followed. The sample size was calculated using the standard formula. Sample Size was 400, for having better analysis it was taken as 500 in each site. But ultimately 998 (496 from Chankharpool and 502 fro Shyamoli) TB suspects were included).

Study tools and data collection:
A semi -structured standardized questionnaire was used for data collection. Two interviewers for each study centre were selected from the staff of the

respective centre. Interviewers were provided orientation training on interview and data collection techniques which was followed by pre-testing. The patients for pre-testing were other than the study patients. Before interviewing, informed consent was taken. Every day, after collection of data following questionnaires by the interviewers, submitted to supervisor who rechecked and submitted to the National Coordinator on regular basis. Data were collected from mid July – mid September 2005. The data sheets were sent to SAARC TB centre through courier service for entry and analysis.

Data entry and analysis:

In STC a data base was prepared in SPSS 2003 soft ware programme and the colleted data were entered then the analysis was done. The level of statistical significance was defined as *p* d" 0.05.

Quality assurance:

For quality assurance, data collection was supervised by the supervisors & coordinator. Before entering into the data base all the filled up questionnaire were checked. Four confusing data sheets were rejected and 998 valid cases were analyzed.

Results

The results of the study were as follows:

- **Socio-demographic Profile of the TB Suspects**

Sex and age

Over all male : female ratio was 1:8 and number of male TB suspects was more in Chankarpool in comparison to Shyamoli (*p*=0.038), (Table 1).

Age of more than 52% of the studied TB suspects was below 30 years and more than 84% were below 60 years. Higher number of females was found in the age group of 15-19 years. Beyond that age group, males were more and this difference was significant in the age group of 30 years and above. Overall mean age was significantly higher in male TB suspects (35.15± 14.9) in comparison to that in female TB suspects (28.77± 12.84), (*p*<001), (Table 2 & Figure 1).

Table 1 Distribution of the TB suspects by sex and study site

Study site	Male (%)	Female (%)	Total (%)
TB Control & Training Institute, Chankharpool	298 (60.1)	198 (39.9)	496 (49.7)
NTCP, Shyamoli	269 (53.6)	233 (46.4)	502 (50.3)
Total	**567 (56.8)**	**431 (43.2)**	**998 (100)**

Table 2 Distribution of TB Suspects by Age and Sex

Age Group	Male	Female	Total
15-19	64(39.3%)	99(60.7%)	163(16.3%)
20-29	190(52.8%)	170(47.2%)	360(36.1%)
30-39	108(59.3%)	74(40.7%)	182(18.2%)
40-49	87(63.5%)	50(36.5%)	137(13.7%)
50-59	57(78.1%)	16(21.9%)	37(7.3%)
60+	61(73.5%)	22(26.5%)	83(8.3%)
Total	567(56.8%)	431(43.2%)	998(100%)

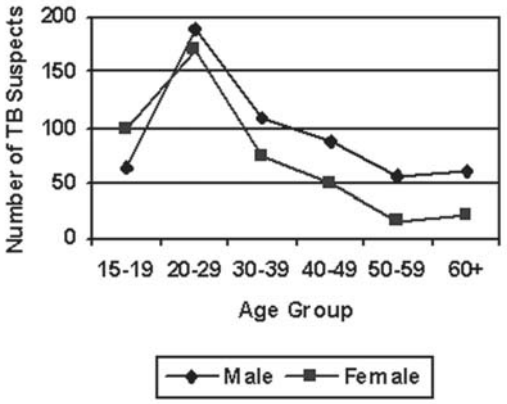

Figure 1 Age and sex distribution of the TB suspects

Area of residence

Majority (nearly 68%) of the respondents was from urban area and 19% were from rural area. Other 13% were from semi-urban or slum area. There was no sex difference among the place of residences of the TB suspects. (*p* >0.05)

Table 3 Distribution of the TB suspects by sex and area of residence

Place of residence	Male (%)	Female (%)	Total (%)
Rural	123(64.7)	67 (35.3)	190 (19.0)
Urban	371 (54.8)	306 (45.2)	677 (67.8)
Semi-urban	44 (57.9	32 (42.1)	76 (7.6)
Slum	29 (52.7)	26 (47.3)	55 (5.5)
Total	**567 (56.8)**	**431 (43.2)**	**998 (100)**

Marital status

More than 64% of the TB suspects were married and 27.5% were unmarried (Table 4).

Table 4 Marital status of the TB suspects

Status	Frequency	Percent
Married	643	64.4
Unmarried	274	27.5
Divorced/separated	26	2.6
Widowed/widower	55	5.5
Total	**998**	**100**

Education

Table No. 5 shows that 35.5% of the TB suspects were non- educated and 52% had education below SSC level. Only 12.5% had education of SSC level or above.

Table 5 Education of the TB suspects

Status	Frequency	Percent
No education	354	35.5
Up to IV	110	11.0
Class V to VII	257	25.8
Class VIII –IX	152	15.2
SSC	56	5.6
HSC	48	4.8
Graduate & above	21	2.1
Total	**998**	**100.0**

Occupation

Of the total respondents 431 were females and among those females 221 were housewives, which comprised the highest proportion (22.1%) of occupation among the total respondents. Working in garments or other industries was the next common occupation with total number of 208, and among them 63% were females. Day laborer or unskilled laborer comprised 8.8% and all of them except 3 were males, (Table 6).

Table 6 Occupation of the TB suspects

Occupation	Male (%)	Female (%)	Total (%)
Farming /Agriculture	40	0	40 (4.0)
Business	84	1	85 (8.5)
Service –professional/Technical	32	3	35 (3.5)
Service -general	68	6	74 (7.4)
*Driving (including service)	29	0	29 (2.9)
Industry or Garment worker	77 (37.0)	131 (63.0)	208 (20.8)
Day laborer/unskilled labor	85	3	88 (8.8)
Rikshaw/Van/ Thelagari puller	55	0	55 (5.5)
Student	32	33	65 (6.5)
Housewife	0	221	221 (22.1)
Tailor	10	2	12 (1.2)
House servant	0	16	16 (1.6)
Unemployed	40	15	55 (5.5)
Others (hawker, mason, hairdresser, cobbler)	15		15 (1.5)
Total	**567 (56.8)**	**431(43.2)**	**998 (100)**

* Driving as regular service is not included in service

Family size

The total number of family members varied from 1 to 14 with mean and median values of 5.27± 2.08 and 5.00 respectively. Majority (57.3%) of the TB suspects in this study were from a family having 4-6 members. About 23% were from a family of 7-10 members (Table 7).

Table 7 Family size of the TB suspects

Number of family member	Frequency	Percent
1-3	183	18.3
4-6	572	57.3
7-10	227	22.7
11-14	16	1.6
Total	**998**	**100.0**

Income

During interview data on total monthly family income was collected (Table 8a). Because of different family size, per capita monthly family income was computed later on (Table 8b). About 58% of the studied TB suspects were from families having per capita monthly income of less than 1000 BDT(Bangladesh Taka) (US $ 15) and 91.5 % were from families having per capita monthly income of less than 2000 BDT (US $ 30).

Table 8a Total monthly family income

Income (BDT)	Frequency	Percent
500-2000	137	13.7
-3000	262	26.3
-4000	150	15.0
-5000	154	15.4

-7000	162	16.3
-10000	95	9.5
-15000	29	2.9
"20000"	7	0.7
"30000"	2	0.2
Total	**998**	**100**

Table 8b Per capita monthly family income

Income (BDT)	Frequency	Percent
<500	143	14.3
500 – 749	269	27.0
750 - 999	163	16.3
1000 – 1499	252	25.3
1500 - 1899	86	8.6
2000 – 2499	44	4.4
2500 – 3999	27	2.7
4000 – 7500	14	1.4
Total	**998**	**100**

Table 9 Average values of age, family size and family income of the TB suspects

Variables	Mean (Sd.)	Median	Mode
Age	32.39 (14.4)	28	20
Family size	5.27 (2.08)	5	4
Monthly total Family income (BDT)	4770 (3135)	4000	3000
Monthly per capita Family income (BDT)	1001.79 (748.5)	800	1000

Presenting Symptoms of the TB suspects

Along with cough, other complaints were chest pain (87%), fever (82%), night sweat (62%), loss of appetite (86%), loss of weight (89%) and blood stained sputum (33%).

Compared to males higher number of females complained of fever (p <0.05), chest pain (p <0.05) and loss of appetite (p <0.05), (Table 10).

Comparison of average (mean) durations of symptoms between two sexes shows that females were suffering for longer duration but these differences are not statistically significant except night sweat (p =0.044), (Table 11).

Table 10 Distribution of TS by gender and presenting symptoms (N=998)

Symptoms	Sex	No (%)	Yes (%)	*p* Value
Cough	male	0	567	
	female	0	431	
Fever	male	119 (21.0)	448 (79.0)	0.007
	female	62 (14.4)	369 (85.6)	
Night sweat	male	220 (38.8)	347 (61.2)	0.444
	female	157 (36.4)	274 (63.6)	
Chest pain	male	90 (15.9)	477 (84.1)	0.005
	female	42 (9.7)	389 (90.3)	
Loss of appetite	male	92 (16.2)	475 (83.8)	0.012
	female	46 (10.7)	385 (89.3)	
Loss of weight	male	63 (11.1)	504 (88.9)	0.234
	female	38 (8.8)	393 (91.2)	
Blood stained sputum	male	378 (66.7)	189 (33.3)	0.606
	female	294 (68.2)	137 (31.8)	

Table 11 Comparison of average duration of symptoms between two sexes

Symptoms	Sex	Number with symptoms	Mean duration	Std. Deviation	*p* Value
Cough	Male	567	116.11	121.65	NS
	Female	431	112.74	100.41	
Fever	Male	448	93.08	93.94	NS
	Female	369	97.64	84.79	
Night sweat	Male	347	68.44	69.30	.044
	Female	275	80.97	85.42	
Chest pain	Male	477	97.79	114.78	NS
	Female	389	101.69	108.07	
Loss of appetite	Male	475	88.92	87.53	NS
	Female	385	92.78	82.73	
Loss of weight	Male	504	95.76	92.90	NS
	Female	393	101.91	88.78	
Blood stained sputum	Male	189	31.98	56.75	NS
	Female	137	39.07	88.56	

Health seeking behavior and barriers in health seeking of the TB suspects

About 17 percent of the respondents did not take any advice for their symptoms before visiting the centre. There was no significant gender difference in this regards (Table 12). In more than 52% cases, the cause for not taking advice was ignorance (means

they did not consider the problem so serious), The other causes were lack of time/ busy with house hold work (15%) and want of money for travel (31.7%). Two TB suspects mentioned "service not free of cost' as cause for not taking health advice. After merging the last 2 causes χ^2 test was done and found no significant sex difference in cause for not seeking health care (Table 13).

Out of 831 TB suspects who sought advice for their symptoms, 349 (42.0%) visited paraprofessionals or irrelevant sources e.g. Village doctors, Pharmacists, medicine sellers, homeopaths, local health workers etc. About 35% visited qualified private practitioners, about 3% visited private hospitals and 4 % visited NGO run health centres. Only 137 (16.5%) visited government hospitals/health posts. No significant gender difference was found in source of Health seeking (p>.05), (Table 14).

Table 12 Advice taken by the TB suspects before visiting the study centre

Sex	Advice taken		
	No (%)	Yes (%)	Total
Male	99 (17.5)	468(82.5)	567 (56.8)
Female	68 (15.8)	363 (84.2)	431 (43.2)
Total	**167 (16.7)**	**831 (83.3)**	**998 (100)**

Table 13 Cause for not taking advice by the TS

Sex	Considered Problem not serious / ignorance	Lack of time /Busy with household work	Want of money for travel	Service not free of cost	Total
Male	54 (54.5)	12 (12.1)	32 (32.3)	1 (1.0)	99 (59.3)
Female	33 (48.5)	13 (19.1)	21 (30.9)	1 (1.5)	68 (40.7)
Total	**87 (52.1)**	**25 (15.0)**	**53 (31.7)**	**2 (1.2)**	**167 (100)**

Figures in parenthesis indicate percent

Table 14 Place/source of taking advice by the TS

Sources	Male	Female	Total
Nonqualified/irrelevant source Pharmacist/medicine seller	190(40.6)	140(38.6)	330(39.7)
Local health worker	12(2.6)	7(1.9)	19(2.3)
Qualified Private Practitioner	157(33.5)	132(36.4)	289(34.8)
Private Hospital	11(2.4)	12(3.3)	23(2.8)
NGO run Health Centre	18(2.8)	15(4.1)	33(4.0)
Govt Hospital/ Health	80(17.1)	57(15.7)	137(16.5)
Total	**468(56.3)**	**363(43.7)**	**831(100)**

Figures in parenthesis indicate percentage

Difficulties faced

The respondents were asked whether they had faced any difficulties or problems in visiting the centre. In response to wage loss for visiting the centre, significantly higher proportion of males (40.2%) said yes in comparison to that of females (26%), (p <0.001). Regarding need of accompanying person, significantly higher proportion of females (81%) said yes in comparison to that of males (60%), (p <0.001) (Table 15).

About one-fourth (26%) of the total respondent responded as "yes" when asked whether they were aware about the nature of their illness and in this regard there was no sex difference. All of these respondents mentioned their illness as "probably TB" except two – one as "probably cold" and other as "probably pneumonia". Compared to female higher proportion of males tried to hide their illness (39.3% Vs 32.7%, p=0.032), (Table 15).

A total of 36 (3.6%) and 43 (4.3%) positive responses were obtained regarding exclusion from participation in social events and feeling of rejection by family/ friends respectively. Only two respondents gave positive responses for both. Therefore all together 75 (7.5%) of the respondents have faced either of these problems (Table 15).

The TB suspects under this study faced no problems (as they mentioned) in getting advice in the study centres.

Table 15 Difficulties faced in visiting the study centre or in the family or society due to the illness (N=998)

Difficulties	Sex	No (%)	Yes (%)	*P* Value
Wage loss	male	339 (59.8)	228 (40.2)	< 0.001
	female	319 (74.0)	112 (26.0)	
Need of accompanying person	male	227 (40.0)	340 (60.0)	< 0.001
	female	82 (19.0)	349 (81.0)	
Awareness about nature of illness	male	423 (74.6)	144 (25.4)	0.646
	female	316 (73.3)	115 (26.7)	
Illness discussed with others	male	223 (39.3)	344 (60.7)	0.032
	female	141 (32.7)	290 (67.3)	
Excluded from participation in social events	male	546 (96.3)	21 (3.7)	0.851
	female	416 (96.5)	15 (3.5)	
Feeling of rejection by family/friends	male	541 (95.4)	26 (4.6)	0.621
	female	414 (96.1)	17 (3.9)	

Discussion and conclusion

This cross sectional institution based study was conducted by STC in two TB diagnostic centres in Dhaka City Corporation to explore the health seeking behaviour and barriers in seeking health with gender differentials among identified TB suspects. The study reveals that more than two third of the TS were from urban area and overall socioeconomic status of most of the TS was poor. These findings are in favor of the well established fact that TB is primarily a disease of the poor especially who are living in over crowded environment of the urban area.[7] Overall mean age was much higher in male TB suspects than that in female TB suspects. This is because of higher number of females in the age group of 15-19 years and higher number of males beyond that age group. NTP reports also reveal more or less similar pattern of age & sex distribution among the reported TB cases.[3, 10] In a community based study done by STC the average age was also higher in case of male TS, though not significant and might be due to smaller sample size. [9]

About 17% of the respondents gave no history of previous health seeking for the symptoms and the common causes for not seeking health care were ignorance or lack of awareness and want of money for travel. Forty-two percent of those who gave previous history of health seeking visited para-professionals or nonqualified private sources. About 38% visited qualified private doctors or private hospitals. No significant gender difference was found either in cause for not seeking health care or in sources of health seeking. The community based study done by STC also revealed similar types of findings.[9] A study on health seeking behaviour among household members of aged 20 years or more in rural Bangladesh also revealed that the most commonly consulted type of health provider was a paraprofessional such as a village doctor, a medical assistant or a community health worker without any significant age or gender difference.[11]

Significantly higher proportion of male TS had to loose their daily wages. This might be due to the fact that more males are engaged in daily or contract basis work outside their houses and females are mostly engaged in household works which do not account wages. On the other hand significantly higher proportion of female TS had to take an accompanying person for visiting the centre. This reflects the prevailing socio-cultural situation in the study area, where female usually do not want to go alone outside their houses.

Recommendations

- For effective implementation of DOTS strategy, awareness development programme for paraprofessionals needs to be strengthened and sustained with special attention to Pharmacists or medicine sellers
- More emphasis is to be given on public private partnership which is crucial for achieving case detection target.
- Similar type of study needs to be repeated in different areas/ countries

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GENDER AND TB CONTROL
ECONOMIC BURDEN ON TB PATIENTS PRIOR TO RECEIVING DOTS IN NEPAL

Tara S Bam[1], **Robert S Chapman**[1], **Donald A Enarson**[2]

[1]*College of Public Health, Chulalongkorn University, Bangkok, Thailand*
[2]*International Union Against Tuberculosis Lung Disease (The Union), Paris, France*

Abstract

Setting: Kathmandu valley (Bhaktapur, Kathmandu and Lalitpur)

Objective: To document the gender differences economic burden on tuberculosis patients prior to receiving treatment under DOTS.

Methods: Face to face interviews, using a standardized questionnaire, were conducted among 379 male and 237 female TB patients, who were enrolled at 37 randomly selected DOTS centres between January to August 2006. Direct medical cost (consultation fees and money spent on investigations and medications), direct non-medical costs (money spent on travel, lodging, and food and special foods), indirect cost (loss of wages due to illness), and total costs (expenditure incurred under direct and indirect costs) were calculated. Incomes were calculated based on the information given by the patients. Descriptive and bivariate analysis was done.

Results: Of the 616 people interviewed, 379 (61.5%) were male and 237 (38.5%) were female. The mean (SD) age in years was 34.28 (+14.90) for male and it was 30.10 (+13.14) for female. The mean total direct expenditure attributable to consultation, diagnosis and medication of tuberculosis for male and female patients was Nepalese rupees 1,933 and Nepalese rupees 2,306 respectively. These medical costs accounted 34.7% of the mean monthly income for males and 57.1% for females. Indirect costs were calculated only for 169 male and 70 female patients. The mean indirect cost was Nepalese rupees 5,706, which was NRs. 5,555 for male patients and NRs. 6,070 for female patients. The average total cost for males was NRs 4,682 and it was 4,381 for females. For males, this cost represented to 84.1% of the mean monthly income and it was 108.4% for female patients.

Conclusion: Direct and indirect costs were incurred significantly high among female patients due to the several encounters with private practitioners. The costs incurred due to the poor follow up of standard diagnosis and treatment procedures & delayed referral behavior among the private practitioners which could be minimized only private practitioners were integrated into the system.

Key words: economic-burden, gender, TB, Nepal

Introduction

Tuberculosis can be prevented and treated. However, tuberculosis (TB) continues to be a leading cause of morbidity and mortality worldwide. It kills more than 2 million people each year.[1] In Nepal, it is estimated that approximately 5,000–7,000 people die from TB and about 20,000-25,000 active pulmonary tuberculosis patients occur every year, of whom 60% are of economically productive age. In 2004, it was reported that the notification rate of new smear pulmonary positive TB was 56/100,000.[2] Published studies suggest that tuberculosis affects the most productive age group and resulting economic cost

Correspondence to:
Tara S Bam
College of Public Health,
Chulalongkorn University,
Bangkok, Thailand.
E-mail: tara_bam@yahoo.com

for society is high.[3] It was documented that female often face obstacles in accessing to diagnostic services, investigations and gaining adequate information. They often face triple burden of housework, caring children, and senior members of the household, and allowing little time from the employment for their health care.[4] Studies in the Uganda[5] and the Thailand[6] reported that patients bear more than 60% of the total burden of tuberculosis costs. Furthermore, half of the monetary costs and the majority of time lost from work are incurred before diagnosis. The cost burdens of health care may deter or delay health care utilization or promote use of less effective health care sources or practices by the poor in general and by the women in particular. It was published that poor households more frequently opted for care outside the modern sector than better off households, and that the cost of TB or malaria treatment, as well as distance to health facilities, were significant barriers to access for poor households.[7,8]

Early diagnosis and early treatment are the important elements of the successful TB control programmes. Delay in diagnosis may worsen the disease, increase patient expenditure, increase risk of death, and enhance TB transmission in the community.[9,10] Thus the propose of the present study is to document the gender differences in economic burden on patients accessing to TB diagnosis & treatment and also to provide the information to policy-makers to better understand regarding patient barriers to accessing services.

Nepal is one of the poorest countries of the world. Its annual per capita gross national product (GNP) is US$ 389 with 38% of the population living on less than US$1 a day. The health care delivery system of Nepal is complex. Health care delivery remains largely the responsibility of the Ministry of Health, although private medical systems are increasingly providing health services, particularly in the urban areas. The government health care system is consisted of sub health post for every 1000 population, health post for every 20-30,000 population and primary health care centre for every 100,000 population, providing essential care services to their catchment's people, while the district, zonal, and regional hospitals are the secondary referral units, and the national hospitals are the tertiary care level hospitals, established in the urban settings. Both qualified and non-qualified private providers are in easy access to the patients particularly in urban areas. They charge their patients for their services; the cost is always higher compared to government facilities.

This study was conducted in the Kathmandu valley, where DOTS strategy is universally applied for TB treatment. At the time of study, there were 70 DOTS centres already in existence and functioning. The valley accounts 7.2% of the total national population and about 18% of the national estimated TB cases.[2] The estimated annual risk of TB infection (ARTI) is 4% of this place which is twice of the rest of the places of the country.[2] About 52% of the male estimated TB cases have been detected and enrolled in DOTS in these districts, while the corresponding figure for female was 32% in the year 2004.[2] A DOTS centre is available approximately between 20 to 30 minutes traveling time by public transportation. The majority of its population has good geographical access to DOTS system.

Methods

Study population and data collection

Thirty-seven DOTS centres were randomly selected. New smear positive pulmonary tuberculosis patients registered in the NTP between January and August 2006, were study subjects. The interviews were conducted monthly using structured questionnaire. A total of 674 new smear positive TB patients were enrolled during the study period. Direct interview was conducted among 616 patients (379 males and 237 females). There were 58 (8.6%) refusals.

Cost estimates

Direct costs

Consultation fees and money spent on investigations and medications were classified as medical expenditure. Money spent on travel, lodging, and food and special food were classified as non-medical expenditure.

Indirect costs

Indirect costs were classified as loss of wages due to illness. Decreased earning ability due to illness, or long term disability that necessitated changes in type of work were not included in this study. Thus it was one of the limitations of our study.

Total costs

Total cost covered expenditure incurred under direct and indirect costs between the time intervals of onset of symptoms and initiation of treatment. The cost was calculated in terms of Nepalese rupees and US dollars (exchange rate at the time of study was 1 US$ = 70 Nepalese rupees).

Incomes were calculated based on the information given by the patients. During the interviews, patients were asked about the loss of work days during their illness. Costs were calculated as percentages of patients' mean monthly income. Indirect costs were computed only for working male and female patients.

Statistical analysis

Univariate analysis of the variables was performed using SPSS version 13. Chi-square test was used. A *P* value <0.05 was considered significant.

Results

Patient characteristics

Of the 616 people interviewed, 379 (61.5%) were male (62% of them married), and 237 (38.5%) were female (59% of them married). The mean (SD) age in years was 34.28 (14.90) for male and it was 30.10 (13.14) for female. Majority of the male (77.1%) and female (83.9%) respondents were between the age group of 13 to 44 years old, which is considered the most productive and reproductive period of the life time.

One fifth (19.3%) of the male patients and 40.9% of the female patients had no education, while 20.3% of the male and only 12.7% of the female patients had the higher level of education. Occupation wise the male and female patients comprise 124 (32.7%) and 62 (26.2%) laborer, 5 (1.3%) and 79 (33.3%) housework, 55 (14.5%) and 47 (19.8%) students respectively and the rest belonged to different occupational groups. Sixty percent of the male (377) and 19.2% of the female (234) patients identified themselves as the major source of income for their household, and the proportion was significantly different between the male and female (p<0.001).

Overall 342 of the study subjects, the median monthly income from all sources was Nepalese rupees 4,500 (mean = 5118), which is equivalent to US$ 60. The median monthly income was significantly different between male and female patients (p<0.001). It was 4,850 Nepalese rupees (66 US$) for male and 3,000 Nepalese rupees (40.5 US$) for female patients. Of the 88 female respondents who reported some sort of monthly income, 67% (59) had their monthly income less than median (NR 4,500), while this proportion was 49.6% (126) of the male patients (254). Median dichotomization of the monthly income was observed significantly difference between male and female as well (p = 0.005).

Regarding the annual household income of the 616 respondents, 74.5% reported their annual households' income (male 85.8% and female 56.5%). The median annual households' income was found 60,000 Nepalese rupees (810 US$) overall as well as for both male and female patients. The overall mean annual households' income was NRs.87836 (male NRs. 95307, female NRs. 69716). The mean rank of the annual households' income was found significantly different between male and female patients; it was 185.47 for male and 131.18 for female (p = 0.011).

Cost data

Direct cost:

Table 1 shows the mean total direct expenditure attributable to consultation, diagnosis and medication of tuberculosis for male and female patients as Nepalese rupees 1,933 and Nepalese rupees 2,306 respectively. The mean direct cost incurred by patients was Nepalese rupees 2,077. These medical costs accounted 34.7% of the mean monthly income for male patients and 57.1% for female patients. Seventy percent of the mean monthly income of the male patients expended to private physician and private nursing home, while this proportion was 92.8% of female patients. Regarding non-medical costs, the mean non-medical cost was Nepalese rupees 321 and 314 for males and females respectively. There was a significant difference between the groups (p=0.021). It was incurred 5.8% and 7.8% of the mean monthly income of the male and female patients respectively.

Table 1 Patient tuberculosis cost data

Variable	Male n	Mean	Mean % MMI*	Female n	Mean	Mean % MMI*	All n	Mean	Mean % MMI*
Direct expenditure									
Medical									
Nursing Home	52	2122	38.1	42	2235	55.3	94	2173	42.0
Private physician	92	1790	32.1	66	1515	37.5	158	1676	32.4
Traditional healers	18	1166	20.9	54	1216	30.1	72	1203	23.2
Public facility	327	967	17.4	197	992	24.5	524	977	18.9
Private pharmacy	141	837	15.0	116	752	18.6	257	799	15.4
Ayurvedic	10	229	4.1	8	431	10.7	18	319	6.2
Spiritual	1	10	0.2	2	300	7.4	3	203	3.9
Total medical	379	1933	34.7	237	2306	57.1	616	2077	40.1
Non-medical									
Transportation	280	191	3.4	191	202	5.0	471	196	3.8
Food	128	173	3.1	62	176	4.4	190	174	3.4
Additional food	208	104	1.9	117	95	2.4	325	101	2.0
Lodging	31	190	3.4	13	468	11.6	44	276	5.3
Total non-medical	321	321	5.8	213	314	7.8	534	318	6.1
Indirect costs									
Lost income									
Total	169	5555	99.8	70	6070	150.2	239	5706	110.2
Farmer	11	4331	77.8	2	1675	41.4	13	3923	75.8
Laborer	82	5230	93.9	48	4809	119.0	130	5074	98.0
Housework	0	0	0.0	0	0	0.0	0	0	0.0
Government service	14	4455	80.0	0	0	0.0	14	4455	86.1
Private service	37	6482	116.4	12	13407	331.7	49	8178	158.0
Student	2	4700	84.4	0	0	0.0	2	4700	90.8
Merchant	14	6228	111.8	7	4185	103.5	21	5547	107.2
No work	5	8100	145.5	1	550	13.6	6	6841	132.2
Others	4	5750	103.3	0	0	0.0	4	5750	111.1
Total patient costs	**379**	**4682**	**84.1**	**237**	**4381**	**108.4**	**616**	**4566**	**88.2**

Indirect cost:

Indirect costs could be calculated only for 169 male and 70 female patients. The mean indirect cost was Nepalese rupees 5,706, which was NRs. 5,555 for male patients and NRs. 6,070 for female patients. The mean lost income due to the illness amounted to 99.8% of the mean monthly income of the male patients, while this loss was 150% of the mean monthly income of the female patients. Of the 169 male and 70 female patients who lost their income, 48.5% and 67.6% were laborers, respectively. The mean lost income by these patients was NRs 5,074 (male 5,230 and female 4,809). These losses were the equivalent of 98% of their mean monthly income (male 93.9% and female 119.0%).

Total cost:

The average total cost was NRs 4,566 (NRs 4,682 in males vs. NRs. 4,381 in females). The average cost of TB to patients was equivalent to 88.2% of patient's mean monthly income. For males, this cost represented to 84.1% of the mean monthly income and it was 108.4% for female patients.

Loss of work days:

Of the 616 patients, 390 (63.3%) reported that they lost work days due to their TB. Of these, 230 (58.9%) were male and 160 (41%) were female. Females had significantly more lost days than males ($p = 0.007$) prior to TB diagnosis. The mean of lost work days was higher among male patients who were unemployed, while for female patients, the number of mean days lost was highest (93 days) for patients reported to be farmers (table 2).

Table 2 Lost work days

Variable	Male n %	Mean	Female n %	Mean	Female n %	Mean
Lost workdays						
Total	230	38.8	160	54.9	390	45.44
Farmer	18 (7.8)	41.0	8 (5.0)	93.1	26 (6.7)	57.08
Private service	39 (17.0)	26.3	12 (7.5)	70.7	51 (13.1)	36.82
Housework	3 (1.3)	34.0	55 (34.4)	57.8	58 (14.9)	56.59
Laborer	82 (35.7)	34.7	51 (31.9)	44.4	133(34.1)	38.50
Student	27 (11.7)	30.3	20 (12.5)	35.2	47 (12.1)	32.38
Merchant	20 (6.5)	34.6	8 (5.0)	21.5	23 (5.9)	30.04
Unemployed	19 (8.3)	99.7	6 (3.8)	14.5	25 (6.4)	110.60
Gov. service	14 (6.1)	26.4	0	0	14 (3.6)	26.43
Others	13 (5.7)	46.8	0	0	13 (3.3)	46.85

Discussion

TB is a major public health problem especially in developing countries. It affects mainly productive and reproductive segment of the population (mostly age between 15 and 59). They are also the parents on whom the survival and development of children and, to an increasing extent the elderly, depend. The present study also documented that 84% of the female and 77% of the male patients were between the age of 15 to 44 years old with mean 34 for male and 30 for female. The corresponding proportion was very similar with the report of Nepal NTP.[2] Moreover, 61% of the male and 20% of the female patients reported to be a main income earner for the household. It is a great concern how an ill mother suffering with TB make her children healthy. Thus tuberculosis has the potential to obstruct the development of both individuals and the society.[11]

The mean direct cost attributed to consultation, diagnosis and medication for TB related symptoms was Rs. 2, 077. Direct costs were highest by 20% among female (Rs. 2,306) than male (Rs. 1,933) patients. Direct costs were lower among patients attending public health care facilities, and were 6 times higher among patients attending the private sector (sum of costs paid to private physician, private nursing home, traditional healers, and private pharmacy) in both male and female patients. A significant number of patients (female about 75% and male about 87%), although ultimately diagnosed in DOTS centres, incurred heavy expenditure while seeking a diagnosis in the private sectors including traditional healers. It could be due to the fact that a considerable proportion of female patients (81%) made their first visit to private sectors (includes traditional healers) in seeking remedies for their symptoms. Female patients often had several encounters with different providers in the traditional healers, private and public sectors (on average 7.05). Thus reducing the number of health encounters before diagnosis could be one strategy to reduce patient direct cost. These observations hint that although diagnosis and treatment of tuberculosis is offered free of charge to patients attending DOTS centres, a substantial financial loss is incurred prior to attending a DOTS centre. Our findings are consistent with studies from India.[7,12,13]

Our study presents strong evidence for the need to integrate private practitioners, including traditional healers and private pharmacies, into the DOTS program of the National Tuberculosis Control Program. The costs incurred due to the poor follow up of standard diagnosis and treatment procedures among the private practitioners and delayed referral behavior among traditional healers, which could be minimized only if they were convinced to follow the standard policy of TB diagnosis and treatment with respect their contributions toward NTP & if there is strong integration program between NTP & PP.

Non-medical expenditure (costs incurred in travel, food, and special food) also entails a disproportionate burden on the TB patients, especially on poor female patients, as this is also expenditures for out-of-pocket patients. The average non-medical cost was about US$ 5 (Rs. 314) for both male and female patient. This cost is lower than that incurred by Zambian and Indian patients.[7,12] It could be explained by the fact

that our study is mainly on urban setting where a TB diagnosis service is available with median distance of 6 kilometers and about two thirds of them reported, it was accessed within 30 minutes of traveling time by bus. However, the cost would have a great impact on poor female patients.

With tuberculosis, there is loss of productivity and loss of income. The average indirect cost observed for employed patients was Rs. 5706 (US$ 81.5). This cost was higher by 10% among female (Rs. 6070) than male (Rs. 5555). The mean lost income due to TB prior to start of TB treatment was 150% of the mean monthly income of the female patients, and more than two thirds of them were daily paid laborer. The mean work days lost was 55 among female and 38 among male patients prior to start of TB treatment, and it was 45 days for all patients. This is an indirect indicator of the delay in establishing a diagnosis in these patients as reported by Indian study.[12] Similar but general, not gender specific, observations were made by the study from India[12], and Uganda[5], while the very lower days lost (12.5 to 20) was reported from the study of Zambia.[7] We found loss of work days was highest among female farmer patients (93 days). These observations underscore the need for effective educational and advocacy activities, with especial focus on early diagnosis for the female in Nepal.

In the present study, the average total cost was Rs. 4566 (US$ 65.2) prior to start of TB treatment with DOTS. It was Rs. 4381 (US$ 63) for female and Rs. 4682 (US$ 67) for male patients. Interestingly, the cost represents 109% of the mean monthly income of female patients, and the corresponding figure for males was 84.1%. Although aggregate costs for females tend to be lower in real terms than costs for males, costs relative to monthly income are much higher for females than males. NTP Nepal receives about 35,000 TB cases every year.[2] The national loss per year due to expenditure prior to receiving TB treatment (not included caregiver cost, and providers cost) calculates at Rs. 160 millions (US$ 2.3 millions). Furthermore the indirect costs for unemployed persons have not been analyzed and not included in the estimations. It is a great implication for TB control programme. It would be a huge barrier for poor TB patients, especially poor female TB patients, to make advances in early help seeking and early TB diagnosis. DOTS has been reported a cost effective strategy in TB control comparing the cost effectiveness of different primary health care interventions.[14] It has been estimated that now the cost for a basic course of treatment is about US $10 compared with US $40-60 in the early 1990s.[15] One could say it is a cost-effective strategy, producing significant savings for governments and achieving higher cure rates if only patient enrolls voluntarily into the system. But it apparently does not take into consideration the costs incurred by patients before enrolling in the system. The willingness to prompt seeking help could be pressed by the potential expenditures occur during the help seeking journey, particularly poor females who always are resource scare. The free supplies of anti-tuberculosis drugs alone may not be sufficient to improve the early case detection and early treatment. Our findings disclose an urgent need to NTP for collaborative actions with community people including former TB patients, private sector and other community based organizations to promote health educational activities, expansion of DOTS with microscopy facilities (it reduces the travel cost, loss of work days, unnecessary diagnosis and treatment cost), and improved information and communication for the maximum and timely use of the DOTS facilities at the local level.

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SINGLE DOSE PHARMACOKINETICS OF EFAVIRENZ IN HEALTHY INDIAN SUBJECTS

Geetha Ramachandran, A. K. Hemanth Kumar, B. Sukumar, V.Kumaraswami, Soumya Swaminathan

Tuberculosis Research Centre (Indian Council of Medical Research) Chetput, Chennai, India

Abstract

Background & Objective: Access to antiretroviral therapy in India is improving. Efavirenz (EFV) is a commonly used non-nucleoside reverse transcriptase inhibitor used to treat HIV infection. No information is available on the pharmacokinetics of EFV in Indian subjects. The aim of this study was to obtain information on single dose pharmacokinetics of efavirenz (EFV) in healthy Indian subjects.

Methods: Sixteen adult healthy volunteers (8 males and 8 females) were administered a single oral tablet of 600 mg EFV after an overnight fast. Blood samples were collected at 1, 2, 3, 4, 5, 6, 10, 24 and 48 hours post dosing. Plasma EFV concentrations were estimated by HPLC, and certain pharmacokinetic variables were calculated.

Results: Plasma EFV concentrations were higher in females than males at all the time points, the differences being significant at 1 ($p<0.001$) and 2 ($p=0.05$) hours. Females had significantly higher peak concentration (C_{max}) of EFV than males ($p=0.05$) (3.11 & 1.90 µg/ml). The inter-individual variability in C_{max} and AUC_{0-48} were 42 and 45% respectively.

Conclusions: This study provides basic information on the pharmacokinetics of EFV in Indian subjects. Females had higher peak levels of EFV than males. Inter-subject variability was high. Further studies are necessary to describe the pharmacokinetic profile of EFV under steady state conditions in Indian patients on antiretroviral treatment.

Key words: Efavirenz, HIV infection, pharmacokinetics, Indian subjects

Introduction

Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor widely used in the treatment of HIV infection because of its robust antiviral efficacy and relatively good pharmacokinetic and safety profile.[1,2] Current recommendations include EFV in many first-line regimens.[2,3] Variability in response to antiretroviral therapy has been attributed to differences in virologic, immunologic, pharmacologic, and behavioral characteristics.[4] Significant inter-patient variability in the kinetics of antiretroviral drugs has been reported.[5,6] Variability in absorption and disposition of EFV may partially explain the heterogeneity of response to treatment[7]. Some studies have shown a relationship between low and high EFV plasma levels and treatment failure and CNS side effects respectively.[8] Therefore, elucidation of the pharmacokinetic profile of EFV and its variability provides a relevant component of HIV therapeutic optimization.

Correspondence to:
Dr. Soumya Swaminathan
Deputy Director & Head
HIV/AIDS Division
Tuberculosis Research Centre
Mayor V.R. Ramanathan Road
Chetput, Chennai-600 031
Phone: 91-44-28369698
Fax : 91-44-28362528
E-mail: doctorsoumya@yahoo.com

India has a large number of HIV-positive individuals and access to antiretroviral therapy is improving. With increasing number of patients on treatment, it is important to study the pharmacokinetics of commonly used antiretroviral drugs. In addition, differences in EFV pharmacokinetics between various racial / ethnic groups,[9-15] and between males and females[11, 15, 16] have been reported. No information is available on the pharmacokinetics of EFV in Indian subjects, who receive treatment with generic drugs, and who could have genetic differences in the cytochrome P-450 system. We, therefore carried out a study to obtain basic information on the pharmacokinetics of EFV in healthy Indian subjects, following administration of a single dose of 600mg of the drug, which is the conventional dose used to treat HIV-1 infected patients. This would give us an idea about the blood levels of EFV that may be expected in patients who receive treatment with this drug.

Methods

Participants

Sixteen healthy volunteers aged 18 years and above, comprising of 8 males and 8 females took part in the study. All the volunteers were from Tamil Nadu, South India and belonged to the same ethnic group. They underwent physical examination by a medical officer. None of the volunteers was suffering from any illness or taking concurrent medications at the time of the study. The purpose of the study was explained to the study participants and only those willing to participate were included. Informed written consent was obtained from all the study participants before they took part in the study. Smokers, chronic alcoholics and females on hormonal birth control pills were not included in the study.

Drug administration and sample collection

All the volunteers were requested to report to the clinic division of the Tuberculosis Research Centre, Chennai, in the morning after an overnight fast. On the day of the study, about five ml. of blood was collected (0 hour) in a heparinized container. A single tablet of 600 mg EFV (Viranz, Ranbaxy, India) was administered and blood samples (5 ml.) were collected at 1, 2, 3, 4, 5, 6, 10, 24 and 48 hours after drug administration. The total volume of blood collected from each volunteer during the study period was about 50 ml. All blood draws were made from the cephalic vein using an indwelling catheter with heparin lock. Breakfast and lunch were provided at two and six hours of drug administration. The blood samples were centrifuged immediately, plasma separated and stored at –20°C until assay, which was carried out within four days.

Assay Procedure

Plasma EFV concentrations were determined by high performance liquid chromatography (HPLC) (Shimadzu Corporation, Kyoto, Japan) according to the method of Langmann *et. al*,[17] using UV detection set at 246 nm. Efavirenz was extracted into the organic solvent, and the contents were centrifuged at 2500rpm for 10 minutes at ambient temperature. The organic layer was evaporated to dryness, dried residue reconstituted in the mobile phase and injected into the HPLC column. Nefazodone was used as an internal standard. The mobile phase was a mixture of potassium dihydrogen orthophosphate and acetonitrile. The retention times of the internal standard and EFV were 1.8 and 5.8 minutes respectively. Unknown concentrations were derived from linear regression analysis of the peak height ratios (EFV / internal standard) vs. concentration curve. The assay was linear from 0.0625 to 10.0µg/ml with a correlation coefficient value of 0.9992 and limit of quantification of 0.05µg/ml. The intra- and inter-day coefficients of variation were 3.8 and 4.6% respectively, and recovery of EFV from human plasma was 98%.

Pharmacokinetic analysis

On each series of plasma EFV concentrations, certain pharmacokinetic variables were calculated. Maximum concentrations (C_{max}) and the time to attain C_{max} (T_{max}) were determined by direct visual inspection of data. EFV concentration-time data were analyzed by a non-compartmental model using WinNonlin software (Version 5.0.1) (Pharsight Corporation, Mountain View, CA, USA). The log trapezoidal rule was used to compute the exposure or area under the time concentration curve from 0 to 48 hours (AUC_{0-48}). Elimination rate constant (λ) was calculated by applying log-linear regression. This was used to extrapolate AUC to infinity. The apparent oral clearance (Cl) was calculated as dose/$AUC_{0-\infty}$. Half-life ($t_{1/2}$) was calculated by dividing 0.693 by λ, and volume of distribution (V_d) by dividing Cl by λ.

Statistical evaluation

Data were expressed as Median (Range). The significance of differences in the pharmacokinetic parameters between males and females was evaluated by Mann-Whitney 'U' test. A p value of $\leq$ 0.05 was considered statistically significant. Correlation between body weight and that of C_{max} and AUC_{0-48} & $AUC_{0-\infty}$ were tested using Spearman's rank correlation test.

Results

The details of the study participants are given in table 1. Male and female volunteers were similar with respect to age, body weight and dose of EFV normalized to body weight. Plasma EFV concentrations were higher in females than in males at all the time-points tested (Figure 1), the differences being significant at 1 (p<0.001) and 2 (p=0.05) hours. Certain pharmacokinetic variables calculated based on plasma EFV concentrations in male and female volunteers are given in Table 2. Females had a significantly higher C_{max} than males (p=0.05), the median values being 3.11 and 1.90 µg/ml respectively. Mean C_{max} values after normalising to body weight in males and females were 0.036 and 0.055 µg/ml; this difference was also significant (p=0.05). Although $AUC_{0-48\ \&\ 0-\infty}$ and Cl were higher and lower respectively in females than in males, these differences were not statistically significant Overall, the inter-subject variability in C_{max} and AUC_{0-48} was 42 and 45% respectively. There was a negative correlation between body weight and that of C_{max} and $AUC_{0-48\ \&\ 0-\infty}$., but these correlations were not significant.

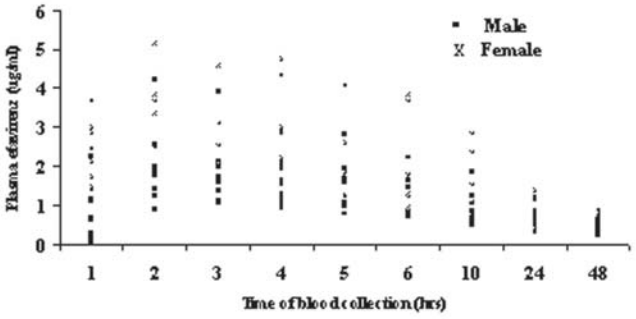

Figure 1 Plasma efavirenz concentration in males (n=8) & females (n=8) at different times points

Table 1 Basic characteristics of study participants

Characteristics	Median (Range)	
	Males (n=8)	Females (n=8)
Age (years)	31(25-52)	35(26-47)
Body weight (kg)	65(53-75)	60(48-65)
EFV dose /kg body weight	9.2(8.0-11.3)	10.0(9.2-12.5)

Table 2 Single dose pharmacokinetics of efavirenz (600 mg) in healthy subjects

Pharmacokinetic Variables	Median (Range)		
	Males (n=8)	Females (n=8)	Overall (n=16)
Peak concentration (µg/ml)*	1.90 (1.41-4.21)	3.11 (1.93-5.15)	2.34 (1.41-5.15)
Time to attain peak concentration (hours)	2.00 (2-4)	2.00 (1-3)	2.00 (1-4)
Exposure $_{0-t}$ (µg/ml. hours)	35.91(20.66-58.89)	47.62 (27.04-88.76)	39.9 (20.66-88.76)
Exposure $_{0-\infty}$ (µg/ml. hours)	64.24 (32.08-100.31)	94.59 (44.72-131.19)	68.36 (32.08-131.19)
Apparent oral clearance (litres/min)	9.53 (5.98-18.7)	6.65 (4.47-13.62)	8.78 (4.47-18.7)
Half-life (hours)	31.77 (23.53-71.71)	41.98 (22.26-74.4)	35.77 (22.26-74.4)
Volume of Distribution(liters)	589.66 (251.56-969.95)	455.09 (167.39-765.46)	525.7 (167.39-969.95)

* denotes *p=0.05*

Discussion

Presently, there are no data available on EFV pharmacokinetics in Indian subjects. This study presents data on certain pharmacokinetic variables of EFV obtained in healthy volunteers, who were administered a single dose of 600 mg EFV. Although considerable data on steady state pharmacokinetics of EFV are available in other populations, there are not many reports available on single dose pharmacokinetics of this drug at a dose of 600 mg. The Sustiva™ product monograph reports a C_{max} of 0.5 to 2.9µg/ml for single oral doses ranging from 100-1600mg in uninfected volunteers[18]. Since these values correspond to a wide dose range, a direct comparison of these values with this study data (Table 2) cannot be made. Howeer, it appears that the median C_{max} of 2.34µg/ml obtained in this study is on the higher side than that reported earlier.[18] Also a T_{max} of 2 hours observed in this study is lower than the earlier report, which implies that the absorption of EFV in the Indian subjects was relatively rapid. Single dose pharmacokinetic data of EFV reported by Reddy *et al*[19] from nine HIV-infected individuals were 2.7µg/ml, 3.5 hours and 29.97µg/ml.hours (median) respectively for C_{max}, T_{max} and AUC_{0-24}. A qualitative comparison of this data with that of our study shows that C_{max} values are almost similar, but T_{max} is shorter in Indian subjects. The AUC values could not be compared since the time periods were different (24 and 48 hours). However, an AUC_{0-48} value of 39.90 µg/ml.hours obtained in our study appears to be higher, given the fact that concentrations of EFV beyond 24 hours were very low. Hence a higher exposure to EFV, and thereby a lower clearance of the drug could be expected in Indian patients infected with HIV. Barrett *et al*[11] have also predicted a lower clearance of EFV in Asians and Africans relative to Caucasians.

Recently, several studies have found that sex can have a modest influence on the pharmacokinetic profile of certain antiretroviral drugs. Potentially sex-specific influences, such as endogenous or exogenous hormones, could impact antiretroviral tolerance, and influence how women respond and react to anti-retroviral. A few observational studies have described a higher frequency of antiretroviral-related adverse effects among women compared to men.[20,21] Sex-related differences in pharmacokinetics of EFV have been reported, with females having 20% higher exposure than males.[15, 16] A lower clearance of EFV in females relative to males has also been reported.[11] Burger *et al*[15] have observed that gender is an important factor in determining variability in plasma EFV concentrations, and they have suggested that one needs to be alert for signs of EFV-induced toxicity in females. A higher C_{max} (even after normalizing to body weight) in females than in males as observed in this study could have implications for patient management, in terms of adverse event profiles. The mechanism for sex-related differences in the pharmacokinetics of EFV, or antiretroviral drugs in general is not clear. It has been suggested that this could be due to the fact that females weigh less and have smaller volumes compared to males. However, in this study, despite normalizing C_{max} to body weight, we still observed a difference between females and males.

Pharmacokinetic differences between patients are an important factor leading to variability in response to antiretroviral agents[6, 22]. High inter-patient variability in EFV pharmacokinetics related to CYP-dependent metabolism and P-glycoprotein-dependent intestinal secretion,[8] and its potential relationship with markers of efficacy and toxicity have been reported.[7, 15] The high inter-subject variability in C_{max} and AUC observed in this study point to the fact that monitoring of plasma concentrations of EFV (therapeutic drug monitoring) may be useful in certain situations.

Efavirenz undergoes metabolism predominantly through CYP2B6. Genetic variability of CYP2B6, in different populations has been reported.[12-14] Variation in CYP2B6 expression among different ethnic groups has also been reported.[12] Race as an important factor in determining inter-individual variability in plasma EFV concentrations has been reported[15]. There are reports of differences in EFV pharmacokinetics a result of single nucleotide polymorphisms in the CYP2B6 gene.[9-11] A 3-fold higher plasma EFV levels in African-Americans than European-Americans has been attributed to a CYP2B6 allelic variant (G516T) that commonly occurs in the black population. This single nucleotide polymorphism was responsible for a lower rate of clearance of EFV in the African-Americans than European-Americans, rendering the former group

more susceptible to CNS side effects.[9] A novel specific CYP2B6 allele (T983C) in Africans has been shown to cause impaired metabolism of EFV.[14]

In the absence of EFV pharmacokinetic data in Indian subjects, this study provides preliminary information on plasma levels that may be expected in patients. A limitation of the study was inadequate sampling time points used to estimate plasma EFV kinetics. Due to the prolonged half-life of EFV, it would have been ideal to estimate drug levels up to 360 hours. However, in this study, due to logistic reasons, we could not collect blood samples after 48 hours. Generally, pharmacokinetics of drugs could change in disease states, and it is not easy to extrapolate the pharmacokinetic parameters from healthy subjects to patients. Hence pharmacokinetic studies of EFV in HIV-infected patients on antiretroviral treatment in India are required. This would enable us to examine relationships between EFV pharmacokinetics, efficacy and CNS toxicity. Further studies are also necessary to determine whether genetic polymorphisms in drug metabolizing enzymes, particularly CYP2B6 influence EFV disposition in this population. It would also be worth exploring sex-related differences in tolerability and adverse reactions among patients, as there is some suggestion from our study that females have higher peak and drug exposure levels of EFV.

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BLINDED RECHECKING OF SPUTUM AFB SMEARS IN RNTCP, INDIA: ANALYSIS OF LOT QUALITY ASSURANCE SAMPLING DATA OF NINE STATES SUBMITTED TO NATIONAL REFERENCE LABORATORY FOR THE YEAR 2006

Ajay Kumar T, Kumar P, Chauhan L S, Balasangameshwara V H, Shyni S & Shiju S

National Tuberculosis Institute, Bangalore, India.

Abstract

Setting: National Tuberculosis Institute, Bangalore and RNTCP sputum smear microscopy laboratory Network, India.

Objective: To analyze basic LQAS data of nine states for the year 2006 submitted to National Reference Laboratory.

Design: The details of rechecking data were obtained from 4810 Designated Microscopy Centers, in a prescribed format, in nine states for the year 2006. Data was collected from NRL on site evaluation reports, periodic reports from Intermediate Reference Laboratories and Designated Microscopy Centers (DMCs) and laboratory registers. Data analysis was carried out at NRL.

Results: Average annual slide volume in a DMC for negatives and positives were 1819 and 225, respectively. Average slide positivity rate for Acid fast bacilli (AFB) was 12.4%. Based on the RNTCP recommended LQAS sample size table, annual minimum rechecking sample was 530937 (6%) of total slide volume. Calculated average minimum sample to be rechecked in a district TB center (DTC) was 175 slides. Average duration required for rechecking at DTC level was 5-6 days in a month, and for each controller was 1-2 days. LQAS sample size for 3512 DMCs (73%) lied within ANSV lot and SPR ranges of RNTCP recommended LQAS sample size table. State-wise analysis of DMCs indicated that State-B had 10% of DMCs under <300 ANSV with <5%SPR. State-C had high percent (22.7%) of DMCs with >1000 ANSV <5% with SPR. State-G had high proportion of DMCs for both the above SPR and ANSV criteria. These states and DMCs required programme intervention to ensure better accessibility of the laboratories to people, sufficiently trained medical officers & lab technicians, maintaining quality of binocular microscopes and improved/adequate referrals for sputum examination. Monthly sample size of d”8 slides was employed in 1485 DMCs (30.8%); d”12 slides was employed in 3074 DMCs (63.9%); and d”18 slides was employed in 3841 DMCs (79.8%) DMCs.

Conclusion: The analysis established base-line information on the performance parameters and identified DMCs where programme intervention was required for improvements. Estimated overall annual sample based on LQAS indicated that RNTCP recommended LQAS annual sample size had valid statistical coverage of 100%, within the set performance goal, and no substantial decrease in work-load compared to a uniform sample size of 8, 12 or 18 slides per month per DMC. RNTCP recommended annual sample size based on LQAS methodology for random blinded rechecking was appropriate and operationally feasible.

Keywords: Acid fast bacilli; Annual negative slide volume; External quality assessment; Lot Quality Assurance Sampling; Random blinded rechecking; Slide Positivity Rate.

Correspondence to:
Dr. P. Kumar
Director,
National Tuberculosis Institute, Avalon,
No. 8 Bellary Road, Bangalore-560003. India.
Ph: 91-080-23362431,
Fax: 91-080-23440952.

Introduction

Sputum smear microscopy for the detection of smear positive pulmonary tuberculosis cases and their follow-up for treatment is an important component of RNTCP. For every one lakh population, one Designated Microscopy Center (DMC) and one trained LT has been ensured by the RNTCP for the diagnosis of the TB.[1] An interdependent hierarchical network of laboratories composed of District Level Lab (DTC), state level lab (IRL) and National Reference Lab (NRL) has been established to undertake the external quality assessment (EQA) of the smear microscopy laboratories.[2],[3] Central TB division at New Delhi, along with three National Reference Laboratories, 27 state level intermediate reference Laboratories and 11963 peripheral DMCs form the RNTCP laboratory network.[2],[4] NRLs provide technical guidance on EQA data obtained from IRLs and DMCs and conduct supervisory visits for ensuring effective quality assured sputum microscopy laboratory network in the country.[5] NTI as NRL has been allotted responsibility to supervise ten states in India for EQA and all DMCs under these states.

Components of EQA at the peripheral level are (a) check-list based on-site evaluation (OSE) of laboratories and (b) Random blinded reexamination (RBRC) of routine DMC smear.[6] Systemic errors in the laboratories are identified through OSE and RBRC are solved by exploring possible causes, probable solutions and timely implementation of corrective measures. Random Blinded rechecking is a process of rereading a randomly selected sample of slides (comprising both positive and negative smears) from peripheral laboratories (DMCs) by controllers at a higher level laboratory (DTCs) for evaluating performance of laboratories for quality improvement.[6,7] Lot quality assurance sampling (LQAS) sampling strategy is adopted based on certain set criteria instead of sampling 10% of negatives and 100% of positives for rechecking. LQAS method allows determination of an optimum statistically acceptable samples size to assess quality of work of the laboratory technicians and laboratory network.[8]

This paper analyzes the basic data obtained for the year 2006 by NTI from allotted nine states on implementation of LQAS based RBRC in India. The results establish base-line information on the performance parameters and identify the proportion of DMCs where programme intervention was required for improvements.

Methodology

LQAS based annual and monthly sample (table 1) of slides to be reexamined at DMCs is determined by RNTCP based on set criteria of 80% sensitivity, 100% specificity, '0'acceptance number (d) and 95% confidence levels.[2] Employing d=0 and a predetermined performance goal (80% sensitivity), if a DMC has no false negatives then there is assurance within a 95% confidence interval that the laboratory has met the sensitivity goal. False positives represent system errors. 'Lot' specifies total number of negatives prepared in a year. LQAS sample size for each DMC was determined based on Annual negative slide volume (ANSV) and slide positivity rate (SPR) (total annual positive slides*100/total slide volume).[6]

Data pertaining to year 2006 was submitted by nine allotted states-Orissa, Rajasthan, Maharastra, Madhya Pradesh, Jharkhand, Karnataka, J&K(Kashmir division), West Bengal, and Pondicherry. The details of rechecking data were obtained from 4810 DMCs (95.7%) out of a total 5026 in nine states. There are 11963 DMCs in India, at the end of 2nd quarter 2006, thus the data represents 40.2% of DMCs in the country. For the sake of anonymity, the nine states in the investigation were coded as states A - I. Data was also gathered from NRL EQA On site evaluation reports, IRLs' periodic reports to NRL, DMCs' periodic reports to IRL and laboratory registers. The reporting formats were as per the RNTCP revised EQA guidelines. Data analysis was carried out at NRL employing PivotTable tool of MS-office-Excel spread-sheet software.

Results

Compiled data from 4810 reporting units in nine states showed a total of 87, 52,158 slide volume. Average annual slide volume in a DMC for negatives and positives were 1819 and 225, respectively. Average slide positivity rate for Acid fast bacilli (AFB) was 12.4% (table 2). Based on the recommended LQAS sample size table (table 1) annual minimum rechecking sample was 530937 (6%) of total slide volume in the

DMCs. Calculated average minimum sample to be rechecked in a district TB center (DTC) was 175 slides (table 2).

The cross-tabulation of DMCs as function of ANSV lot and SPR range showed that while sample size for 3512 DMCs (73%) lied with in ANSV lot and SPR ranges recommended by RNTCP- LQAS table (Table1), 1298 DMCs (27%) had either <5% SPR and <300 ANSV or both (table 3). DMCs with >5% SPR plus >500 ANSV were 2862 (59.5%) of total reported DMCs.

State-wise analysis of DMCs reporting <300 ANSV with <5% SPR compared to >1000 ANSV with <5% SPR showed that State-B had 10% of DMCs under <300 ANSV with <5%SPR but no DMC under >1000 slides with <5% SPR. State-C had high percent (22.7%) of DMCs with >1000 ANSV <5% with SPR. State-G had high proportion of DMCs for above SPR and ANSV criteria (table 4).

Distribution of monthly LQAS sample size among the reporting DMCs from nine states showed that monthly sample sizes of d”8 slides was employed in 1485 DMCs (30.8%); d”12 slides was employed in 3074 DMCs (63.9%); d”18 slides was employed in 3841 DMCs (79.8%) DMCs (table 5).

Estimates of work-load of minimum rechecking sample load based on LQAS strategy options showed that recommended RNTCP LQAS annual sample size (table 1) has statistical coverage of 100% in nine states and comparatively less sample loads than a uniform sample size of 8, 12 or 18 slides per month per all DMCs (table 6-Option 1). A uniform sample volume of 9 slides, monthly per DMC, calculated based on average SPR and ANSV load in total reporting DMCs was able to reduce the sample load by only 2.2% (table 6- option 3). While the non-LQAS based frequently used sample size of all positives and 10% negatives had 71.3% more work load than LQAS based recommended sample size (table 6-option 4).

Table 1 RNTCP recommended LQAS based Annual Sample Size for DMCs for RBRC *

ANSV	SLIDE POSITIVITY RATE (SPR%)†				
	2.5-4.9	5.0‡-7.49	7.5-9.9	10-14.9	≥15
301-500#	243 (21)	154 (13)	114 (10)	89 (8)	62 (6)
501-1000	318 (27)	180 (15)	128 (11)	96 (8)	66 (6)
>1000	456 (38)	216 (18)	144 (12)	104 (9)	69 (6)
CV for false negatives (at minimum)	0.65%	1.32	2.03	4.41	>4.41

*Based on LQAS method applied to the negative slides with sensitivity of 80%, specificity of 100%, Acceptance number d=0, and 95% Confidence Interval. Each sample size was then increased proportional to the positivity rate to yield the final sample size that includes both positive and negative slides. Annual sample size of both positive and negative slides

† Monthly sample size is given in parenthesis. The monthly sample size has been rounded off to the next higher number and annually adds up to equal or more than the annual sample size.

‡ DMCs with less than 5% SPR should analyze the reasons for the same and should undertake the necessary corrective actions.

If the ANSV is less than the indicated Annual Sample Size (ASS), the respective DMCs should submit all their slides for blinded re-checking. Till their status is finalized, those DMCs with ANSV less than 301 will use the sample size for 301-500 ANSV as applicable for the respective SPR range. *For example, a DMC with ANSV <243 & SPR <4.9%, or ANSV <154 & SPR 5.0-7.5%, or ANSV <114 & SPR 7.49-9.9%, or ANSV <89 & SPR 10-14.9%, or ANSV <62 & SPR ≥15% should submit all slides for blinded re-checking.*

Table 2 Analysis of basic data from nine states allotted to NTI for year 2006

Serial	Parameter	Data
A	Total DMCs included in analysis	4810
B	Total smears/slides (annual)	8752158
C	Total Positive smears/slides (annual)	1084553
D	Total Negative smears/slides (annual)	7667605
E	Average annual DMC total slide volume	1819
F	Average annual DMC negative slide volume	1594
G	Average annual DMC positive slide volume	225
H	Slide Positivity Rate	12.40%
I	Number of STLS	941
J	Number of DTCs	254
K	Total slides to be cross-checked (actual in year 2006)	530937
L	Expected rechecking slide load per DTC per month =(K/J) DIV 12	175
M	Calculated minimum time to be spent on RBRC per district per month: (L+ expected 10% of discordance) (175+17) DIV (@40 slides per day)	5-6 days
N	Calculated minimum time to be spent on RBRC by a STLS per month: (K/I) DIV 12 = 48 slides	1-2 days

Table 3 Distribution of Number (percent) of DMCs based on- 'Lots' of Annual negative slide volume (ANSV) and Slide positivity rate (SPR) range among nine allotted states

	SLIDE POSITIVITY RANGE (SPR)						
ANSV	**<2.5%**	**2.5-4.9%**	**5-7.5%**	**7.5-10%**	**10-15%**	**>15%**	**Total**
<300	131(2.7)	69(1.43)	123(2.55)	127(2.64)	219(4.55)	223(4.63)	892(18.54)
301-500	51(1.06)	44(0.91)	49(1.01)	78(1.62)	117(2.43)	125(2.59)	464(9.64)
501-1000	125(2.59)	109(2.26)	177(3.67)	206(4.28)	252(5.23)	206(4.28)	1075(22.34)
>1000	230(4.78)	128(2.66)	404(8.39)	547(11.37)	682(14.17)	388(8.06)	2379(49.45)
Total	537(11.16)	350(7.27)	753(15.65)	958(19.91)	1270(26.40)	942(19.58)	**4810(100)**

SPR =Slide positivity rate; ANSV=annual negative slide volume; Data of State Bihar has not been reported; RBRC sample size for year 2006. In LQAS size calculation, previous years SPR and ANSV are employed.

Table 4 State-wise distribution of number and Percent of DMCs with <5% SPR and ANSV of <300 or >1000 (subset of table 3)

State	Total number of reporting units (DMCs) (100%)	ANSV	
		<300	**>1000**
A	504	8(1.6)	10(2.0)
B	711	71(10.0)	0.0
C	1090	53(4.9)	247(22.7)
D	659	25(3.8)	13(2.0)
E	254	5(2.0)	4(1.6)
F	613	6(1.0)	38(6.2)
G	115	27(23.5)	8(7.0)
H	852	3 (0.4)	37(4.3)
I	12	2(16.7)	1(8.3)
Total	**4810**	**200 (4.15)**	**358 (7.44)**

Table 5 State-wise distribution of number of DMCs in comparison to monthly RBRC-LQAS sample size load for year 2006 (for NTI states) #

State	RBRC slides to be verified per month Vs Number of DMCs*				
	8 slides DMCs	12 slides DMCs	18 slides DMCs	27 slides DMCs	38 slides DMCs†
A	185 (36.71)	366 (72.62)	441 (87.50)	490(97.22)	504(100)
B	464 (65.26)	464 (65.26)	559 (78.62)	711 (100.00)	711(100)
C	171 (15.69)	504 (46.24)	651(59.72)	678 (62.20)	1090(100)
D	322 (48.86)	507 (76.93)	590 (89.53)	626 (94.99)	659(100)
E	53 (20.87)	197(77.56)	233 (91.73)	241 (94.88)	254(100)
F	129 (21.04)	389 (63.46)	526 (85.81)	566 (92.33)	613(100)
G	14 (12.17)	26(22.60)	46(40.00)	67(58.20)	115(100)
H	146 (17.13)	616 (72.30)	789 (92.60)	812 (95.30)	852(100)
I	1 (8.30)	5 (41.60)	6 (50.00)	6 (50.00)	12(100)
Total	**1485 (30.8%)**	**3074 (63.9%)**	**3841 (79.8%)**	**4197 (87.2%)**	**4810 (100%)**

Total number of DMCs at the end of 2q 2006 allotted under NTI states=5747. The sample size is fixed for whole year based on ANSV and SPR for the year 2005. Data from Bihar was not available. * Figures in the Parenthesis indicate the per cent (%) of DMCs. † Maximum number of sample slides as per LQAS table of EQA guidelines document (table 2, page 29). This equals to total number of reporting DMCs.

Table 6 Estimates of minimum annual sample for RBRC

Option	Sample size selection		Number of slides to be verified in 4810 DMCs per annum	% DMCs coverage for LQAS method (as given in table 5)
1	Uniform Number of slides/ month/ DMC	8 slides	461760	30.8
		12 slides	692640	63.9
		18 slides	1038960	79.8
2	LQAS size per annum* (RNTCP actual for year 2006)		530937	100
3	LQAS sample size based on national average @12.4 SPR and >1000 slides per DMC		519480	<63.9%
4	All positives & 10% negatives		1851313	n/a

* based on table 1 and 3

Discussion

Random blinded rechecking of a sample of routine patient smears of a laboratory is considered the best reliable method for evaluating performance and assuring that a country has an effective AFB microscopy network to support DOTS.[6,7,8,1] RNTCP has implemented country-wide blinded rechecking of slides, based on LQAS annual sample, assessed every month, as a part of EQA.[2] Starting from year 2005, operational and technical issues of planning and implementation such as capacity of labs to store the slides in slide boxes, trainings of laboratory supervisors to systematically collect LQAS sample slides from DMCs and re-read them after blinding, trainings of DTOs to supervise RBRC process, capacity of state level labs (IRLs) to supervise rechecking by conducting regular and periodic on-site evaluations, and compilation and reporting to national reference labs has been strengthened. As a result, RNTCP laboratory network established blinded rechecking of AFB sputum smears with improved staffing, trainings, microscopes, internal quality controls, supplies and performance reportings.[3,5]

Sampling of 10% of negatives and 100% of positives has been discontinued and RNTCP has adopted LQAS based method for sampling the slides for rechecking. Based on statistical parameters of 80%

sensitivity, 100% specificity, '0' acceptance number and 95% confidence interval, a simplified LQAS sample size table was provided for rechecking.[2]

This paper analyzed basic LQAS data of year 2006 of nine states, as a part of responsibility of NRL to provide technical guidance to EQA programme. The analysis of results of blinded rechecking programme, in terms of type and quantity of errors identified, and their impact on improving the performance of labs would be assessed with a long-term perspective and hence has not been provided in this paper.

The present analysis of 4810 DMCs in nine states, indicated that average annual negative slide volume in a DMC was 1819 and SPR of 12.4% with approximately 50% of DMCs with more than 1000 annual negative slides. The calculated average work-load per staff for rechecking at DTC level was 5-6 days in a month, and for each controller was 1-2 days. More than 42% of DMCs had ANSV of >1000 slides with SPR of e"5% where as DMCs with <300 slides with SPR of <5% were 4% of the total indicating that reasonably sufficient volumes for successful rechecking program based on LQAS methodology. State-wise analysis of DMCs of <300 ANSV with <5% SPR indicated that programme intervention in improvements for states G, H and I were needed for providing better accessibility of the laboratories, trained medical officers and increased referrals for sputum examination through expansion of public-private mix programmes. Like-wise the DMCs of >1000 ANSV with <5% SPR in the State-C indicated that improvements in internal quality of reagents, maintaining quality of binocular microscopes, technical trainings to Lab staff and referral of only eligible chest-symptomatic for sputum examination.[2] The list of these DMCs with problem would require adequate attention from the programme supervisor and managers.

Operational feasibility of overall rechecking sample size was analyzed. Overall monthly LQAS sample loads indicated that at the minimum 18 slides per month are required to obtain coverage of statistically valid sample size in approximately 80% of DMCs. The results of rechecking programme from the remaining 20% of DMCs would not be eligible for LQAS analysis. Selvakuamr et al., suggested the implementation in the field of LQAS of eight slides per month per microscopy centers based on the LQAS based assessment of 12 microscopy centers (assuming 10% SPR and ANSV of >1000 slides) for blinded rechecking from Thiruvallur district of Tamil Nadu, India.[3] However, the present data analysis of 4810 DMCs for valid sample size by LQAS method indicated only 30% coverage of total DMCs by assuming 8 slides/ month per DMC. Moderated estimations of overall annual sample load based on LQAS options indicated that the RNTCP recommended table for sample size not only extends validity of minimum sample size to all DMCs for analysis of result but also provides operationally feasible lesser slide-load for rechecking.

Conclusions

This paper analyzed basic LQAS data of nine states, as a part of responsibility of NRL to provide technical guidance and feed-back for random blinded rechecking programme. The data represents 40.2% of DMCs under RNTCP in India for the year 2006. Average annual AFB negative slide volume in a DMC was 1819 and SPR of 12.4%. Approximately, 50% of DMCs had more than 1000 annual negative slides. The calculated average duration required for rechecking at DTC level was 5-6 days in a month, and for each controller was 1-2 days. Reasonably sufficient slide volumes for LQAS based rechecking programme existed in DMCs. Certain states and DMCs where programme intervention was required were identified to ensure better accessibility of the laboratories to people, sufficiently trained medical officers & lab technicians, maintaining quality of binocular microscopes, and improved/adequate referrals for sputum examination. RNTCP recommended annual sample size based on LQAS methodology for random blinded rechecking was appropriate and operationally feasible.

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A CASE OF SUCCESSFUL PROSECUTION OF A DEFAULTER IN ANURADHAPURA DISTRICT OF SRI LANKA

Waidyaratne RADKM Deepthini[1], **Waidyaratne DL**[2]

[1]*Chest Clinic, General Hospital, Anuradhapura, Sri Lanka.*
[2]*General Hospital, Anuradhapura, Sri Lanka.*

Abstract

Tuberculosis is a devastating disease, infecting about a third of the global population and causing an estimated two million deaths every year. In 2002 there were about 8.8 million new cases of tuberculosis, of which 3.9 million, had infectious pulmonary disease, maintaining the cycle of transmission. Left untreated, pulmonary TB may, not only lead to serious complications and to death, but also causes an existing threat of spread of the disease. Partial treatment of TB leads to development of multi drug resistant (MDR TB) form of the disease, adding further burden to the public health of the society.

National programme for tuberculosis control and chest diseases has been working hard to achieve highest levels of cure rate in Sri Lanka through implementing DOTS strategy and by minimising default. This unique case presented here illustrates how the legal provisions of existing penal laws of the country, concerning public health and safety were utilised to persuade a patient who had been defaulting after few days of treatment of direct smear positive pulmonary tuberculosis, to oblige with the full course of Anti TB Treatment. This is the first case of this nature in Sri Lanka.

The public health issues as well as legal and ethical considerations related to the problem are discussed.

Key words: MDR-TB, fight against default, defaulter

Introduction

As a part of actions of national programme for tuberculosis control and chest diseases to achieve the highest levels of cure rate of tuberculosis in Sri Lanka through implementing DOTS strategy and by minimising default, an attempt was made to bring a notorious defaulting patient back to treatment through legal action. The unique case presented here illustrates how the legal provisions of existing penal laws of the country, concerning public health and safety were utilised to persuade a patient who had been defaulting after few days of treatment of direct smear positive pulmonary tuberculosis, to oblige with the full course of ATT. This is the first case of this nature, in Sri Lanka.

Correspondence to:
Dr. RADKM Deepthini Waidyaratne
Chest Clinic, General Hospital
Anuradhapura, Sri Lanka
E mail: kmdr@slt.lk

According to Senaratne, who had treated 14 MDR-TB cases in Sri Lanka from November 1997 to August 2002, previous treatment episodes of 81% of those patients had been either irregular or defaulted.[4]

The public health issues as well as legal and ethical considerations related to the problem are discussed.

Short history of the case

Mr. SMRB. Age: 71 years, Male from a sub-urban village of Anuradhapura was admitted to a Medical ward, General Hospital, Anuradhapura in March 2005. He was presented with cough more than 3 months and haemoptysis. Later he was referred to Chest Clinic and diagnosed to be suffering from pulmonary tuberculosis smear positive (New Case). Patient was

registered in the District TB Register. However, he refused to take recommended anti TB treatment and left the hospital against medical advice on following day.

Actions taken

DTCO and the members of Public Health staff visited his residence and explained the gravity of illness, requested and persuaded him to take treatment. The visits were repeated on several occasions and three months later, in June 2005, he ultimately agreed to take treatment. But, he refused even to visit the nearest DOTS centre or to take inward ATT. This particular person happened to be so miserable that neither the health volunteers nor the other responsible members of the local society agreed to be a DOTS provider for him. No other option was left other than the PHI of the area to carry the drugs daily to his door step and observe him taking them, which too was agreed upon and the drug supply was arranged. He started taking drugs on 25.06.2005, but abruptly discontinued treatment on 15.08.2005 claiming that he was not ill of TB.

This situation led to an impending further public health hazard as discontinuation of anti TB treatment could result in developing multi drug resistant TB (MDR TB). Subsequent visits to his home by DTCO and public health staff to convince him were fruitless.

As the ultimate resource, in the interests of the society, a legal action was sought under the provisions of sections 262 and 263 of the Penal Code of Sri Lanka, concerning the offences against public health and safety. After a brief trial, the Magistrate's Courts issued an order binding the patient to undergo a full course of inward anti TB treatment.

Patient was admitted to the TB ward at Anuradhapura General Hospital and first four months he underwent an intensive closely observed course of ATT. Later with the consent of the Courts, ambulatory DOTS was arranged for the rest of category II regimen at nearest health institution as the patient was co-operating adequately by that time.

Patient was cured at the end of course of treatment and now looks well. Never the less he didn't forget to thank the health staff.

Ethical Considerations

Basically, present day medical treatment is almost exclusively voluntary. Patient's autonomy is considered the far most significant value in ethical debate.[3] That means, no doctor is supposed to 'treat' a human being without his or her consent or against his or her will. The particular patient, involved in this case under discussion, refused treatment at a certain point of time in the course of his treatment.

On the other hand the patient himself was a native physician – practising their own ancestral version of native medicine, who had little trust in western medicine. There had been a number of villagers seeking treatment for various minor ailments, from him.

Discontinuation of ATT halfway, while still being smear positive, posed an existing threat to public health of the locality, escalating the risk of developing MDR TB and spreading the disease. The nature of occupation of the patient as a native physician, which warranted him to have close contacts with the public made this risk even greater. This particular patient, himself attended the hospital when he was badly ill, complied with initial treatment but refused the same once his condition was improved with treatment. This action was due most likely to the stigma of 'being labelled of TB patient', which he would have thought to be damaging to his social image as a native doctor. Considering these facts it was decided to seek legal sanction to impose compulsory treatment as provided for by the law of the land.

This case illustrates another aspect of medical ethics, confidentiality of patient's information. The existing system of TB control service of the country involves exposure of patients to a great extent. Admission to well known 'TB ward' and attending TB clinic could have been seen as stigmatizing by some of the patients. This can be a deterrent to diagnosis as well.[6] This case shows the need of a new approach that respects individual rights of confidentiality and privacy to make patients feel easier and comfortable when seeking treatment for suspected TB. Such an approach associated with wide public education might improve case detection through voluntary self referrals.

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Case Report: Changes in Immune Parameters of a Patient with HIV and MDR TB following Chemotherapy and Adjunctive Immunotherapy

N. Thapa[1,2], J. L. Stanford [3]

[1,2] Immunologist, Department of Medicine, Institute of Biomedical Sciences, K U, Medical School, Nepal.
[3] Department of Bacteriology, Royal Free and University College Medical School, London, UK.

Abstract

Dual infections with HIV and *M. tuberculosis*, especially multi-drug resistant strains lead to poor outcomes. HIV and MDR-TB negatively affect chemotherapy against each other. The present case report described the effect of adjunctive immunotherapy to activate the cell-mediated immunity by switching Th2→ Th1 immune response using an immunoadjuvant prepared from autoclaved *M. vaccae*. Following adjuctive immunotherapy the patient became sputum-negative for M. tuberculosis. This suggests that adjunctive immunotherapy has an important role in the treatment of mycoabacterosis, particularly drug-resistant types in HIV-positive patients.

Introduction

There has been a resurgence of tuberculosis following the advent of the HIV infection. Both HIV and tuberculosis show defective cell-mediated immunity as shown by the reductions of the proportions of CD4 T cells out of CD3 T cells and CD3 T cells out of total lymphocytes.[1] Patients with HIV with and without tuberculosis also show impaired Th1 response and elevated Th2 response.[2] Th1 cytokines such as IFN-gamma and IL-2 activate macrophages and hence activate the cell-mediated immunity[3] whereas Th2 cytokines such as IL-4 inhibit macrophages while enhancing humoral response involving antibody production by B cells[4].

Similar immune dysfunctions are also seen in HIV-positive and HIV-negative patients with pulmonary tuberculosis.[5] HIV positivity also leads to increased susceptibility to tuberculosis and atypical mycobacterioses as well as other opportunist pathogens such as *Pneumocystic carinii*[6]. The burden of both HIV and *M. tuberculosis* severely impairs the immune system, resulting in increased morbidity and mortality. Discovery of new generation drugs for HIV have improved outcome of these patients. However, the emergence of multi-drug resistant *M. tuberculosis* (MDR-TB) has complicated the chemotherapeutic treatment of patients with dual infections. This case study describes a patient with HIV and MDR-TB following adjuctive immunotherapy, after he failed to respond to anti-tubercular treatment.

Correspondence to:
Dr. Navin Thapa
Department of Medicine
Institute of Biomedical Sciences
Kathmandu University Teaching Hospital
Dhulikhel, Nepal
Tel: 009771-5535514
E-mail: n.thapa@ku.edu.np

Case report and Discussion

A forty-four years old male HIV +ve was suspected to have acquired multi-drug resistant tuberculosis (MDR-TB) from another patient. These MDR-TB strains were found to develop further resistance to different antimycobacterial drugs. This patient did not respond to antitubercular therapy and his sputum remained acid-fast bacilli (AFB) positive in spite of three years of chemotherapy. He was being treated with zidovudine, DDC, protease inhibitor as well as ciprofloxacin. He was started on M. vaccae adjuctive immunotherapy of two fort-nightly doses followed by three two-monthly doses. Materials and methods for intracellular cytokine detection has been previously published in the SAARC Journal of Tuberculosis, Lung Diseases and HIV/AIDS, 2005; 2 (1)

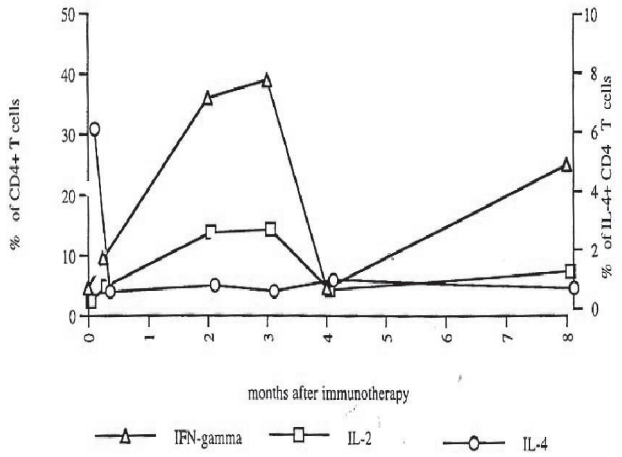

Fig. IFN-gamma, IL-2 (left axis) and IL-4 (right axis)

Prior to immunotherapy, this patient had elevated intracellular Th2 and reduced Th1 cytokines detected intra-cellularly following *in vitro* stimulation with PMA and ionomycin for four hours. He also had very low levels of *M.tuberculosis*-specific IgG, indicating that Th2 response does not necessarity enhance the production of antimycobacterial humoral immune response. His proportion of B cells was less than 1% of total lymphocytes which is far lower than the normal range of healthy people (5-10%). His IL-4 production by CD4 T cells dropped after the first dose of immunotherapy.

Interestingly, his CD4:C8 T cells ratio also dropped from 0.67 to 0.40 after the first dose of immunotherapy before increasing slightly after the second dose to 0.53. Tuberculosis patients have been found to have a reduction in their CD4 T cells and an increase in their CD8 T cells, resulting in the reduction of their CD4:CD8 ratio.[7] Tuberculosis patients with more severe diseases such as those with chronic disease refractory to chemotherapy were found to have a lower CD4:CD8 ratio compared to newly diagnose drug-sensitive tuberculosis patients.[8] Furthermore, the CD4:CD8 ratio of tuberculosis patients were found to return to normal levels following chemotherapy. The changes in the balance of CD4 and CD8 T cells could have occurred as a result of their differential synthesis, release, apoptosis or emigration into the sites of disease. The CD4:CD8 ratio has been reported to be altered in the pleural fluid and broncho-alveolar lavage samples compared to the peripheral circulation of tuberculosis patients.[9] The change in proportions of CD4 and CD8 T cells has also been reported to occur as a result of external antigenic challenge. It is also not known whether the reduction of CD4:CD8 ratio precedes pathogenesis of tuberculosis or if it is the result of the disease itself.

HIV patients with lover CD4 T cell counts show an increased susceptibility to tuberculosis. The frequency of mycobacteraemia increases from 4% in HIV patients with >200 CD4 cells/ml to 49% in HIV patients with <100 CD4 T cells / ml.[10] The superimposition of mycobacterioses is also known to further accelerate the progression of Acquired Immune-deficiency Syndrome (AIDS).

His levels of intracellular IFN-gamma and IL-2 also increased successively after each of the first three doses. His sputum also turned negative for AFB three months after starting adjunctive chemotherapy. However, two months after turning sputum-negative for AFB, this patient suffered from an influenza infection and his Th1 cytokines dropped to their levels before starting immunotherapy. He was an out-patient during this period and no flare up of his tuberculosis or HIV/AIDS symptoms were detected. After the fourth doses of immunotherapy, his IFN-gamma increased again although the levels of IL-2 and IL-4 remained low. He was maintained on chemotherapy to prevent relapse.

Th2→Th1 cytokine switch was seen following *M. vaccae* immunotherapy, involving the increase of Th1 cytokines (IFN-gamma and IL-2), and the decrease of Th2 cytokine (IL-4).

Normally, the drop in the CD4:CD8 T cells ratio, which occurred after the first dose of immunotherapy, would be regarded as unfavourable; however the possible removal of Th2 cells following immunotherapy cannot be ruled out. If this was the case, Th2→ Th1 switch seen after *M. vaccae* immunotherapy might occur by the negative selection of Th2 cells. In fact, the Th1-Th2 cytokine imbalance has been implicated in the activation induced apoptosis of Th2 cells.[11]

Conclusions

This case suggests that the detection of intracellular cytokines provides sensitive assessment of immune profile in HIV and mycobacterioses compounded by additional infections. Furthermore, Th2 Th1 switch could be seen following adjunctive immunotherapy, which might indicate activation of cell-mediated immunity in preference of humoral immunity. The activation of cell-mediated immunity might have been

responsible for the intracellular killing of *M. tuberculosis* as shown by sputum-clearance.

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