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

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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

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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

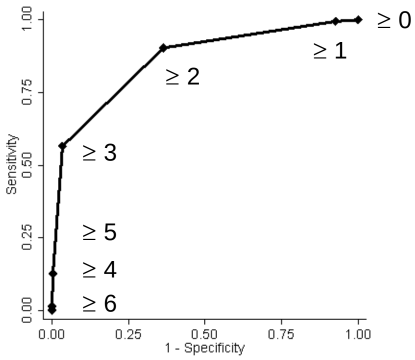

Figure 1a Receiver Operating Characteristics Curve for Model A

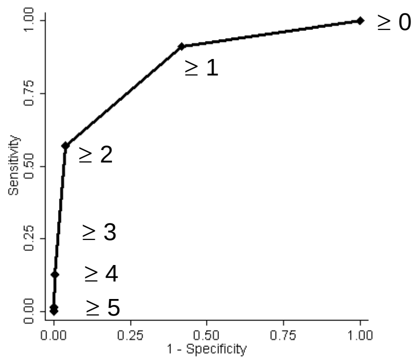

Figure 1b Receiver Operating Characteristics Curve for Model B

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.

Acknowledgement

We thank to the Director of Medical Education, Chennai and the Project Director, Tamilnadu AIDS State Control Society for the constant support and encouragement. We are grateful to Dr. Meade Morgan CDC GAP, Atlanta, Dr. Dora Warren and Dr. Michael Friedman, CDC GAP, India for the funding and for the help in writing the manuscript.

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