



# SAARC

(South Asian Association for Regional Cooperation)

Journal of Tuberculosis, Lung Diseases and HIV/AIDS



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**Published and distributed by:**

SAARC Tuberculosis and HIV/AIDS Centre (STAC)  
Thimi, Bhaktapur  
G.P.O. Box 9517, Kathmandu, Nepal  
Tel.: 00977-01-6632601, 6632477, 6631048  
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The SAARC Journal of Tuberculosis, Lung Diseases and HIV/AIDS is the official journal of the STAC. The Journal's main aim is the continuing education of personnel and the dissemination of the most up-to-date information in the field of tuberculosis, lung diseases and HIV/AIDS. It is devoted to dissemination of knowledge concerning various aspects of tuberculosis, lung diseases and HIV/AIDS. All articles relevant to the practice of this Journal and quality health research are published. The Journal is an appropriate forum for the publication of articles concerning the social, economic, public health, epidemiology, diagnostics, genetics etc. in the area of tuberculosis, lung diseases and HIV/AIDS. The scientific manuscripts presenting the results of public health importance are encouraged. The novel case reports which adds to the existing knowledge and consistent with the scope of Journal will be considered for publication. The Journal accepts review/mini-review, case report, short communications, and letters to editors within the scope of the journal.

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Print ISSN 1818-9741

Online ISSN 2091-0959

# Editorial

## Tuberculosis & Diabetes: need to be addressed

Over the past two decades, TB control programmes worldwide including SAARC region have implemented TB control through DOTS and the Stop TB Strategy with evident success, including substantial increase in rates of case detection and improved treatment outcomes.

To achieve more outcome, innovative plan, policy and implementation at grass root level have to be lunched keeping in mind of best practices, at community level. Similarly, programme has to reach to un-reached population with easy availability of resources at community level so that hidden and unidentified cases can get easy service delivery. In addition, NTP has to address TB not only as a separate disease but its association and impact of other diseases like diabetes & others on it.

Tuberculosis and diabetes mellitus are two major public health problems, which not only often coexist but have serious implication on each other. Diabetes mellitus has an impact on symptomatology, radiological presentation, diagnosis and management of TB.

Tuberculosis (TB) kills more than 3,500 people each day worldwide, leading to approximately 1.4 million deaths every year. One-third of the world's population is currently infected with the causative agent of TB, and 8.8 million new cases of active TB are estimated to occur around the world each year. TB is fueled by several social and economic factors, such as poverty or malnutrition, as well as other infectious diseases, such as HIV.

Diabetes patients are three times more likely to develop of TB when infected. In India alone, 15% of TB is attributed to diabetes. Consequently, rates of TB are higher in people with diabetes than in the general population, and diabetes is a common morbidity in people with TB. Diabetes can worsen the clinical course of TB and can worsen glycaemic control in people with diabetes. Individuals with both conditions thus require careful clinical management. Strategies are needed to ensure that optimal care is provided to patients with both diseases: TB must be diagnosed early in people with diabetes, and diabetes must be diagnosed early in people with TB. Changes in lifestyle and diet have contributed to an increased prevalence of diabetes in many low-income and middle-income including SAARC countries where the burden of TB is high. The growing burden of diabetes is contributing to sustained high levels of TB in the community, and the proportion of TB cases attributable to diabetes globally is likely to increase over time. This double burden of disease is a serious and growing challenge for health systems.

In recent years, strong evidence has been gathered to confirm a link between TB and yet another disease: diabetes mellitus. That link had been suspected for centuries. Many studies now show that diabetes may be associated with an increased risk of developing active TB, and that TB patients who also have uncontrolled diabetes may have higher rates of treatment failure and death.

The World Health Organization, the International Union Against TB and Lung Diseases (the Union), in collaboration with other partners, national TB control programmes developed the Collaborative Framework for Care and Control of TB and Diabetes based on the systematic reviews on the link between TB and Diabetes. Thus, both need to be managed properly at the earliest possible in order to achieve favorable treatment outcomes of tuberculosis by carrying surveillance of TB disease prevalence among people with diabetes and by Intensifying detection of TB among people with diabetes.

TB control programs should also develop educational materials to be distributed at diabetes treatment centers, to inform diabetic patients of their risk of developing active TB. More specifically, symptoms of TB should be clearly highlighted to advise diabetic patients when to seek TB screening. More over the millennium Development goal specifies that the incidence of infectious diseases such as TB should be halted and reversed by 2015. To succeed in achieving this target, it is important to focus on resource-poor countries not only on for HIV/AIDS but also on diabetes as a significant epidemiological risk factor.



## RELIABILITY OF ANTI-MYCOBACTERIAL DRUG SUSCEPTIBILITY TESTING AND IMPORTANCE OF ACCREDITATION OF LABORATORY PERFORMING THE TEST

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### ABSTRACT

**Introduction:** Tuberculosis (TB) is one of the major causes of disease and death in the developing world. World Health Organization recommends that drug resistance surveillance should be carried out regularly in high-burden countries, not only to determine the level of drug resistant TB, but also to strengthen the laboratory capacity. The objective of the study was to evaluate drug susceptibility test (DST) and to observe on DST reports with high variability between the results of two laboratories.

**Methodology:** The study was conducted at Hospital for Chest Diseases and Tuberculosis, SMS Medical College, Jaipur. This was an observational prospective study to analyze DST results, obtained from two different laboratories (Lab A and Lab B), of newly diagnosed sputum positive pulmonary tuberculosis patients registered on DOTS category I. Treatment outcome of patients was obtained from records at the referred clinics and hospitals.

**Results:** Higher proportion of resistance was observed from Lab A (29%) than Lab B (16%), Proportion of MDR strains were higher from Lab A (12.5%) than Lab B (6.0%). Out of the patients whose treatment outcome were available, proportion of patients with treatment success were almost similar in both cohorts (84.6% vs. 85.2%), despite the difference in DST results. Success rate after treatment from Lab A was 60% even in patients with MDR strain, compared to 22% from Lab B.

**Conclusions:** Disparity in DST results was observed from the two laboratories (non accredited and accredited) which does not correlate with the treatment outcome. This study points towards the need of proper quality assurance of the drug sensitivity testing in Mycobacterial testing laboratories.

**Key words:** Tuberculosis, Drug susceptibility, Accreditation, Laboratory

### INTRODUCTION

Tuberculosis (TB) is one of the major causes of disease and death in the developing world. Though modern drug treatment is effective in many cases, emergence of drug resistance especially multidrug resistant (MDR) TB has become a significant public health problem in a number of countries and

a hindrance to effective TB control.<sup>1</sup> In high-burden countries, World Health Organization (WHO) recommends that drug resistance surveillance should be done regularly, not only to determine the level of drug Resistant TB, but also to strengthen the laboratory capacity.<sup>2</sup>

Diagnosis and control of tuberculosis is difficult to achieve as it involves composite measures which may lead to drug related side effects, disruption of daily life, and social isolation. So, it is very important that the methods used to diagnose tuberculosis should be extremely precise.<sup>3</sup> Albeit the development of many newer diagnostic methods, timely and proper use of TB culture may have an impact on TB rates in high-burden countries. Studies have shown that cultures

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of *Mycobacterium tuberculosis* from clinical specimens is presently close to the “gold standard” for diagnosis of TB.<sup>4-7</sup> However, sometimes it can be misleading especially due to the presence of inter-lab variability; it was also interesting to observe that assessment of resistance was different among laboratories, even when the same methods are applied.<sup>8,9</sup>

An erroneous or reprehensible drug sensitivity testing (DST) result may lead to recognition of susceptible cases as resistant or vice versa and may lead to inappropriate or inadequate treatment which may affect the treatment outcome.<sup>8</sup> So, in high burden resource-poor countries, it is essential to carefully prioritize the tools of diagnosis with clinical relevance for maximal utilization of available healthcare facilities. This prospective analysis was conducted to evaluate drug resistance among newly diagnosed sputum positive cases of tuberculosis and to observe if there is any effect of variable DST on treatment outcome of these patients.

## METHODOLOGY

### Setting

The present study was conducted at the Hospital for Chest Diseases and Tuberculosis, SMS Medical College, Jaipur, a large academic hospital serving the population of the western part of India. In the hospital, the diagnosis of pulmonary TB is based on sputum smear microscopy following the National TB Programme recommendations.<sup>10</sup> There is a TB laboratory register where recording of all patients' data along with test results is entered. All TB patients are registered at the hospital DOTS centre, and are referred to specific clinics or hospitals for treatment.

### Design

This was an observational prospective study of newly diagnosed cases of tuberculosis attending outpatient and inpatient department of the hospital, from August 2008 to May 2010. A Structured standard questionnaire was used for the interview, subjects having positive sputum smear were included in the study. Patient with anti-TB treatment history of more than one month of treatment and patients with co-morbidities (diabetes,

renal failure, hepatitis, HIV infection and other immunocompromised diseases) were excluded. Patients were randomized by simple random sampling for sending their sputum specimens to either of the two laboratories performing routine mycobacterial culture and DST, for evaluation to know the initial drug resistance (IDR). After sending sputum samples, all patients included in the study were registered in revised national tuberculosis control programme (RNTCP) and put on treatment under DOTS Category I.

### Laboratory Methods

Pre-treatment sputum samples were sent randomly to the two laboratories. Although it was originally planned to culture two sputum samples per patient, due to logistic and cost constraints only one pretreatment sputum specimen could be collected from each patient and transported to laboratories. Cultures were done on Lowenstein-Jensen (L-J) medium by modified Petroff's method. Cultures were incubated at 37°C and read for growth weekly for eight weeks. Isolates were identified as mycobacteria by smear microscopy and as *M. tuberculosis* by their slow growth rate, colony morphology, inability to grow on L-J media containing p-nitrobenzoic acid (PNB), niacin test and catalase test.<sup>11</sup> DST was carried out by the economic variant of 1 per cent proportion method for all drugs except pyrazinamide which was tested by the resistance-ratio method. The tested drugs and their critical concentrations (in µg/ml) were as follows: isoniazid (H)-0.2, rifampicin (R)-40, pyrazinamide (Z)-100, ethambutol (E)-2 and streptomycin (S)-4.<sup>9</sup> The laboratory methods were uniform as per the standard operating procedure manual, on all samples and in both the laboratories.<sup>11,12</sup>

On availability of DST reports, high variability was observed between the results of two laboratories. Thus, two cohorts were formed on the basis of DST from two laboratories, first cohort (Lab A) with DST from non-accredited laboratory performing routine mycobacterial culture and sensitivity tests and second cohort (Lab B) with DST from accredited intermediate reference laboratory (IRL), where external quality control procedures were in place with monitoring by WHO Supra National Reference Laboratory.



So, Second phase of study was planned, which is the basis of this article; to observe if there is any effect of variable DST on treatment outcome of the patients. Patient from both cohorts were followed at the completion of treatment, and treatment outcome was recorded from treatment register at clinics/ hospitals providing DOTS treatment.

#### Data collection

Hospital and laboratory data were collected by researchers. Names of culture-positive patients were checked against the registrations. Clinic visits were done by two field workers. At least two attempts were made to locate each patient at these follow-up visits made between October 2009 and May 2010.

#### Case definitions

Standard international definitions were used to define the treatment outcomes.<sup>13</sup>

#### Data analysis

The data collected were analyzed by using Microsoft Excel and SPSS (v10.0) computer software. Chi-square and "student- t" test and proportion tests were applied for statistical significance. A *P* value  $\leq 0.05$  was considered statistically significant.

#### Ethics

Permission was obtained from relevant managers and senior clinicians and the study was approved by the Institutional Review Board of SMS medical college, Jaipur, India.

## RESULTS

#### Variability in DST results

Laboratory results were available for 195 specimens from Lab A and 227 specimens from Lab B. A significantly higher proportion of resistance was observed from Lab A than Lab B (29% vs 16%,  $\chi^2 = 9.3$ ,  $p = 0.002$ ) (Table 1). Out of total specimens, cultures were positive in 143 (73.3%) of Lab A and 183(80.5%) of Lab B. Proportion of MDR strains were higher from Lab A (12.5%) than Lab B (6.0%). Lab A reported near to three times rifampicin resistance compared to Lab B (16.7% vs 6.0%,  $\chi^2 = 8.6$ ,  $p = 0.003$ ). A high proportion (4.1%)

of non-MDR rifampicin resistance was detected from Lab A (Table 2).

**Table 1.** Mycobacterial culture and DST results from two laboratories

	Lab A, n (%)	Lab B, n (%)
Specimens tested	195 (100)	227 (100)
Negative culture/contaminated	52 (26.6)	44 (19.3)
Positive culture	143 (73.3)	183 (80.5)
Susceptible to all	86 (44.1)	146 (64.3)
Resistant to at least one drug <sup>#</sup>	57 (29.2)	37 (16.2)

<sup>#</sup>Resistance to the drug in question, either alone or in combination with resistance to others.

**Table 2.** Number of culture-positive patients and drug sensitivity pattern from two laboratories

	Lab A (n=143), n (%)	Lab B (n=183), n (%)
Susceptible to all	86 (60.2)	146 (79.7)
Resistant to at least one drug	57 (39.8)	37 (20.2)
H	39 (27.2)	34 (18.5)
S	29 (20.2)	18 (9.8)
R	24 (16.7)	11 (6.0)
E	22 (15.3)	14 (7.6)
Z	4 (2.8)	2 (1.1)
Multi Drug Resistance	18 (12.5)	11 (6.0)

#### Treatment outcome of culture positive patients

Of the 143 patients with culture-positive results from Lab A and 183 from Lab B, treatment outcomes of 124 and 169 patients respectively from each cohort were available, rest of the patients either did not reported to the referral clinics or were migrated/ transferred out.

#### Treatment outcome and effect of Variability in DST results

Proportion of patients with treatment success (cure/ treatment completed) after completion of DOTS were almost similar in both cohorts (84.6% vs. 85.2%), despite of variability in DST results (Table 3, 4). Also it was almost similar in patients with susceptible strains from both cohorts (89.4% and 91.4%). A higher proportion of success was seen in patients with resistant strains other than MDR from Lab A (86%) than Lab B (78%). More than half of the subjects with MDR strain from

Lab A (60%) got success with DOTS category I, whereas poor success rate was noted among same set of patients from second cohort (22%). Less proportion of patients having MDR strains had adverse outcome (treatment failure/ death) from Lab A (13%) than Lab B (55%), further questioning about DST results from Lab A.

**Table 3.** Treatment Outcome of Patients with DST from Lab A

	TREATMENT OUTCOME			
	Success*	Default	Failure	Death
Sensitive to all (n=66)	59 (89.4)	5 (7.5)	2 (3.0)	-
MDR (n=15)	9 (60)	4 (26.6)	1 (6.6)	1(6.6)
Other Resistance (n=43)	37 (86.0)	2 (4.6)	3 (7.0)	1(2.3)
Total (n=124)	105 (84.6)	11 (8.8)	6 (4.8)	2(1.6)

\* Success = Cured + treatment completed

**Table 4.** Treatment Outcome of Patients with DST from Lab B

	TREATMENT OUTCOME			
	Success*	Default	Failure	Death
Sensitive to all (n=128)	117 (91.4)	8 (6.2)	3 (2.3)	-
MDR (n=9)	2 (22.2)	2 (22.2)	3 (33.3)	2 (22.2)
Other Resistance (n=32)	25 (78.1)	3 (9.3)	3 (9.3)	1 (3.1)
Total (n=169)	144 (85.2)	13 (7.7)	9 (5.3)	3 (1.7)

\* Success = Cured + treatment completed

## DISCUSSION

Findings of the present study showed variation in DST results between the two labs, non accredited lab showing almost double drug resistance compared to accredited lab. On follow up for outcome of treatment, almost similar success and failure rate (Table 3, 4) were observed among patients with drug sensitive and drug resistance (other than MDR) TB, despite of variability in drug resistance results, suggesting that standard SCC regimen had been effective in a majority of patients.<sup>14</sup> The concern was variable outcome in patients with MDR TB, as in the patients with MDR

strain, the initial strain is already resistant to both isoniazid and rifampicin, and virtually there is no drug during maintenance phase of short course chemotherapy (SCC), which possibly results in treatment failure.<sup>15</sup> But good success and less failure rate was noted in these patients with DST from Lab A in contrast to Lab B, which is unlikely in presence of true MDR TB, questioning the reliability of the DST results. Laboratory inaccuracy is also indicated by presence of high rifampicin resistance from Lab A in contrast to Lab B and high (4.1%) non-MDR rifampicin resistance from Lab A. Rifampicin resistance is usually accompanied by isoniazid resistance, presence of isolated rifampicin resistance is very uncommon and good marker for accuracy of laboratory; more than 3% reporting of non-MDR rifampicin resistance indicate errors in either rifampicin or isoniazid testing.<sup>16</sup>

Given the inter-lab variability of the test, poor reliability warrants careful interpretation, as overall response rate of MDR TB is far below that of drug-susceptible TB, if susceptible strains are reported as resistant, regimens may be changed unnecessarily and reserve drugs may be introduced which are more toxic, less potent and more costly than drugs used for primary treatment.<sup>3,17-19</sup>

The main factors which may be responsible to influence DST results include inappropriate standardization of inoculum preparation, impure culture media and improper test environment.<sup>9</sup> Other factors which may be accountable include contamination of clinical devices, clerical errors, laboratory cross contamination, staff shortages relative to the workloads, lack of experience, and most important, failure of the clinician to discuss incongruent results with laboratory staff.<sup>3,20</sup> Accuracy is even more difficult to achieve in countries where skilled manpower and adequate facilities for such tests are scarce.<sup>21</sup>

Present study highlights the fact that improper susceptibility testing for *M. tuberculosis* is not rare and discrepancies are seen between *in vitro* and *in vivo* results and accreditation of laboratories with good quality control should be done to minimize these discrepancies. All laboratories should carry out a thorough internal quality control programme. Analyses and diagnostic services should be accredited with meticulous participation in relevant proficiency schemes to follow strict guidelines and

recommendations. Similarly, where a licensing system exists, laboratories should be licensed to perform TB-related microbiological activity<sup>22</sup>. Standardization of Laboratories is one important step which may help in strict quality control with the purpose of optimizing the clinical relevance of DST results.

These issues call for physicians' attention when using the results from drug-susceptibility testing for case management. The earlier studies providing clinical follow-up of patients with false positive cultures demonstrates a lack of awareness among clinicians and laboratory personnel of the possibility of false-positive cultures and showed that, patients having false-positive cultures were treated for tuberculosis, some of whom experienced toxicity from multidrug tuberculosis treatment.<sup>23-25</sup> First, clinicians should evaluate results of DST critically; and ensure that it should be compatible with patients' clinical response. Second, it should be ensured that DST to be done from standard accredited laboratories, whenever possible and if facilities are not available patient should be referred to higher center. Third and most importantly, patients' clinical response along with sputum conversion should be given an upper consideration before switching on to the regimens based on drug susceptibility.

Some limitations of the study may be taken into account. The main limitation is that the results from only two Laboratories are compared; one of which is accredited and other non-accredited, results would have been more reproducible if more number of laboratories with large sample size were compared. But by comparing the non accredited lab to accredited, we have reinforced the need for accreditation of lab for DST. Further, the possibility of misclassification of retreatment cases as new cases cannot be ruled out, even though proper history was taken and previous treatment records were documented if available. We acknowledge that due to the nature of study design, each laboratory reported on different set of patients and specimens, as randomization of specimen to one or the other laboratory was done; bias could have been introduced if covariates, such as treatment history, age or severity of disease, were associated with certain group of patients. However, proper randomization was carried out using the same testing conditions for

each subject and on comparison between the two groups for general characteristics; no statistically significant difference was observed between the groups. We also acknowledge that to get the exact scenario of DST variability among two laboratories; same samples must be processed by both the laboratories for drug resistance.

Keeping in view the implications of DST in proper diagnosis of MDR TB for effective tuberculosis control, we suggest standardization and quality control of mycobacterial laboratory methods with careful clinical correlation by clinicians for effectual management of MDR TB, curbing the development of drug resistance.

### ACKNOWLEDGEMENTS

The authors express their gratitude to thank Prof. S. P. Agnihotri, MD and Dr. Mahesh Gupta, MD for reviewing the manuscript and constructive suggestions at various stages of the study. We sincerely thank staff of this hospital and also acknowledge the efforts of the health visitors in obtaining the relevant data efficiently and in a short period. This work would not have been successfully completed without the cooperation of all study patients and their family members.

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# GENDER DIFFERENCE ON CASE DETECTION OF PULMONARY TUBERCULOSIS AMONG THE SUSPECTED CASES ATTENDING IN JUTPANI PRIMARY HEALTH CENTRE OF CHITWAN, NEPAL

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## ABSTRACT

**Introduction:** Pulmonary tuberculosis is one of the World's public health problems particularly in developing countries including Nepal. Every year, thousands of people suffered from active tuberculosis in Nepal; of whom 50 percent have infectious pulmonary tuberculosis. It is more common among men than women, and affects mostly adults of economically productive age. There is scantiness of such information in Nepal. Hence the study was carried out to identify the gender difference on case identification of pulmonary tuberculosis in Chitwan district of Nepal.

**Methodology:** Descriptive cross sectional study was carried out from July to December 2012 in Jutpani Village Development Committee of Chitwan, Nepal. All symptomatic cases attending in Jutpani Primary Health Center with the clinical history pulmonary tuberculosis were included. Microscopic examination of sputum samples of three consecutive days was done for AFB. Results were disseminated in tabular, graphical and narrative form using appropriate statistics.

**Results:** Total 200 suspected cases of pulmonary tuberculosis were included in this study; among them 18 (9%) were found to be AFB positive. Sex ratio of diagnosed patients was 5:4 (male; 55.56% and female; 44.44%). Highest prevalence of TB infection (36.89%) was found in 30-40 years age. Highest number of cases 5 (27.78%) were reported in the ward number four (male female ratio; 3:2). One-third of cases were in July followed by 22.22% in each of the month; August and September.

**Conclusion:** Males were found to be more likely to have pulmonary tuberculosis than females. Gender specific case identification and preventive measure targeting to the most productive age group population will eventually supports to reduce the risk of pulmonary tuberculosis.

**Key words:** Pulmonary Tuberculosis, Case Detection, Gender Difference, Suspected Cases

## INTRODUCTION

Pulmonary tuberculosis (PTB) is one of the World's public health threat particularly in developing countries including Nepal.<sup>1</sup> It is the second leading cause of death due to infectious disease

Worldwide.<sup>1-2</sup> Globally; almost nine million new PTB cases had been detected and 1.4 million people died due to the same in 2011.<sup>3-4</sup> India and China; the neighboring countries of Nepal, covered almost 40 percent of the world's tuberculosis cases.<sup>4</sup> Nepal is also vulnerable to such problems and thousands of people suffered from active tuberculosis every year; of which 50 percent have infectious pulmonary tuberculosis.<sup>5</sup> Some gender differentiate have been reported in PTB from different parts of the world; majority are male of productive age group. Nearly twice as many men died from tuberculosis with compare to women. Even so, more women died of TB than from all other

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maternal conditions.<sup>6</sup> Gender inequality has long been identified as a major determinant that can lead to delay in diagnosis, poor access to health care, lack of compliance and also poor treatment outcomes. Health care seeking and treatment behavior of men and women suffering from tuberculosis (TB) is largely determined by how they and those around them perceive the symptoms, regard the diagnosis, accept the treatment, and adhere with it.<sup>7</sup> World Health Organization (WHO) has encouraged gender specific comparisons in TB rates to determine whether women with TB are less likely than men with TB to be diagnosed, reported, and treated.<sup>8</sup> Moreover there is scantiness of such information in Nepal. Hence the study has been carried out to identify the gender difference of pulmonary tuberculosis and its distribution pattern and burden in the rural community of central Nepal.

## METHODOLOGY

A descriptive cross sectional study was carried out in Jutpani Primary Health care Centre (PHC) of Chitwan district, Nepal during July to December 2012. The PHC covers six Village Development Committees (VDC) including Jutpani VDC. Furthermore the VDC has been divided in nine wards as the peripheral level administrative unit by the government of Nepal. All together 200 TB suspected patients from Jutpani VDC visited to PHC during the period of July to December 2012 with the clinical history of two or more week's continuous cough, fever, and marked weight loss were included as the study population. All the potential participants (suspected cases) were briefed about aim of study and oriented for proper collection of the sputum sample. Sputum samples of three consecutive days from all suspected patients were examined microscopically using Z-N staining for Acid Fast Bacilli (AFB) at the PHC.

Due to the inconvenient of sputum sample collection, patients < 10 years of age were excluded from this study. Verbal informed consent was taken before the collection and testing of sample. Ethical clearance was taken from the Institutional Research Board of Central Department of zoology, Tribhuvan University of Nepal. This study was carried out to measure the distribution pattern of pulmonary tuberculosis according to the sex, place and time. Detection of other forms of TB was technically and operationally not feasible in the

DOTS centre. Hence only pulmonary tuberculosis was considered for this study. Brief demographic and clinical history was taken by using the pre designed format (proforma) before collection of sputum sample.

Data accuracy and reliability was maintained by double entry into the SPSS version 20. Percentage, mean, standard deviation and proportion were calculated as univariate analysis and chi-square ( $\chi^2$ ) tests, sensitivity, specificity, and predictive (positive and negative) values were calculated as bivariate analysis. The criterion for statistical significance was set at the value of  $p < 0.05$ . The analyzed data were disseminated in tables, graphs/ charts and narrative form as per necessity.

## RESULTS

All together 200 TB suspected patients (having the age; Mean  $\pm$  SD: 38.1 $\pm$ 9.71 years) were participated in this study. Of which; 18 (9%) were found smear positive and diagnosed as PTB by smear microscopy. Out of total smear positive cases, 10 (55.56%) were male and 8 (44.44%) were female (Table 1). The highest prevalence of sputum positivity (38.89%) was found in the age group of 30-39 years (male positive; 16.67% < female positive; 22.22%) followed by 22.22% in the age group 20-29 years (male positive; 5.56% < female positive; 16.67%). Two age groups (10-20 years and 50-59 years) were found to have the same rate of positivity (11.11% in each ) of total TB positive in grant while there was sex wise differentiation ( male 11.11% and female 0%) in the age group 10-20 years and equal (male : female =1:1) in the other age group 50-59 . The least number of positive cases (5.55%) were found in the other age groups; 40-49 and >70 years respectively (Table 2).

**Table 1.** Gender based positive cases of pulmonary tuberculosis

Sex	Cases (suspected and smear positive)	
	Suspected cases	AFB Positive cases
Male	96 (48.00)	10 (55.56)
Female	104(52.00)	8(44.44)
Total	200(100.00)	18(100.00)

(Note: figures inside the bracket indicate the percentage value)

Table 2. Age and sex wise distribution of suspected and smear positive cases						
Age in years	Male Patients		Female patients		Total suspected cases	Total positive cases
	Suspected cases	Positive cases	Suspected cases	Positive cases		
10- 19	21 (10.50)	2 (11.11)	19 (9.50)	0 (0.00)	40 (20.00)	2 (11.11)
20-29	13(6.50)	1 (5.56)	27 (13.50)	3 (16.67)	40 (20.00)	4 (22.22)
30-39	13(6.50)	3(16.67)	23 (11.50)	4 (22.22)	36 (18.00)	7 (38.89)
40-49	12(6.00)	1(5.56)	13 (6.50)	0 (0.00)	25 (12.50)	1 (5.56)
50-59	20(10.00)	1(5.56)	14 (7.00)	1 (5.56)	34 (17.00)	2 (11.11)
60-69	9(4.50)	1(5.56)	6 (3.00)	0 (0.00)	15 (7.50)	1 (5.56)
≥70	8(4.00)	1(5.56)	2 (1.00)	0 (0.00)	10 (5.00)	1 (5.56)
<b>Total</b>	<b>96(48.00)</b>	<b>10 (55.56)</b>	<b>104 (52.00)</b>	<b>8 (44.44)</b>	<b>200 (100.00)</b>	<b>18 (100)</b>

(Note: Figures inside the brackets indicate the percentage value)

Table 3. Ward wise case detection of PTB on the basis of gender difference						
Ward No.	Male patients		Female patients		Total suspected cases (N %)	Total positive cases (N %)
	Suspected cases (N %)	Positive cases (N %)	Suspected cases (N %)	Positive cases (N %)		
One	17 (8.50)	2 (11.11)	24 (12.00)	2 (11.11)	41 (20.50)	4 (22.22)
Two	6 (3.00)	0 (0.00)	6 (3.00)	0 (0.00)	12 (6.00)	0 (0.00)
Three	8 (4.00)	1(5.56)	4 (2.00)	0 (0.00)	12 (6.00)	1(5.56)
Four	28 (14.00)	3 (16.67)	34 (17.00)	2 (11.11)	62 (31.00)	5 (27.78)
Five	4 (2.00)	1 (5.56)	7 (3.50)	1 (5.56)	11 (5.50)	2 (11.11)
Six	1 (0.50)	0 (0.00)	4 (2.00)	1 (5.56)	5 (2.50)	1 (5.56)
Seven	2 (1.00)	0 (0.00)	4 (2.00)	1 (5.56)	6 (3.00)	1 (5.56)
Eight	19 (9.50)	2 (11.11)	14 (7.00)	1 (5.56)	33 (16.50)	3 (16.67)
Nine	11 (5.50)	1 (5.56)	7 (3.50)	0 (0.00)	18 (9.00)	1 (5.56)
<b>Total</b>	<b>96 (48.00)</b>	<b>10 (55.56)</b>	<b>104 (52.00)</b>	<b>8 (44.44)</b>	<b>200 (100.00)</b>	<b>18 (100.00)</b>

(Note: Figures inside the brackets indicate the percentage value)

In this study the study area has been divided in nine administrative units called wards. Among total 200 suspected cases, 62 (31%) were found in ward number four followed by 21.5%, 16.5% and 9% in ward number one, eight and nine respectively. Fewer cases were suspected in ward number two (6%), three (6%), five (5.5%), seven (3%) and six (2.5%). Similarly out of total 18 smear positive cases, highest prevalence of tuberculosis was found in the ward number four (27.77%) followed by the ward number one (22.22%), eight (16.66%) and five (11.11%). Only one case (5.55%) was diagnosed as smear positive in each of remaining wards (ward number three, six, seven and nine). The male female ratio of pulmonary positive cases

in each of wards from one to nine was 1:1, 0:0, 1:0, 3:2, 1:1, 0:1, 0:1, 2:1 and 1:0 respectively (Table 3).

The study revealed (as shown in figure 1) that the highest suspected cases were found in the month of September in both sexes (female (19.5%) > male (11%)). More or less similar number of cases found in October (male:11%; female 11.5%), November (male:5%; female: 4.5%) and December (male: 8; female:7.5%) where as a lowest number of cases with some of variation in male and female (male (5.5%) > female (3.5%)) found in the month of August. Amongst total smear positive cases, the highest number of positive male cases (22.22%)

found in the month of July measured as double as female positive case (11.11%) in the same month. Similarly the highest female positive cases (16.67%) were detected in the month of October which is three folds more than male positive cases (5.55%) in the same month. Similarly 11.11% of male positive cases were detected in the month of September but no female positive cases were detected in the same time. In the month of August, October, November and December only one (5.55%) positive male case was detected in each month where as 2 (11.11%) and 3 (16.66%) of positive female cases were detected in the same months; August and October with no female

positive cases in November and December (Figure 1).

The study revealed that, there was more than 10% variation in suspected cases of male and female however there was no significant difference ( $X^2=0.452$  at  $df = 1, p>0.05$ ) in gender difference of positivity of pulmonary tuberculosis. The true positive case detection rate (sensitivity) was only 55.55% while the true negative case detection rate (specificity) was 52.74%. Similarly the positive predictive value of pulmonary tuberculosis was only 10.4% meanwhile the negative predictive value was 92.3% as shown in table 4.

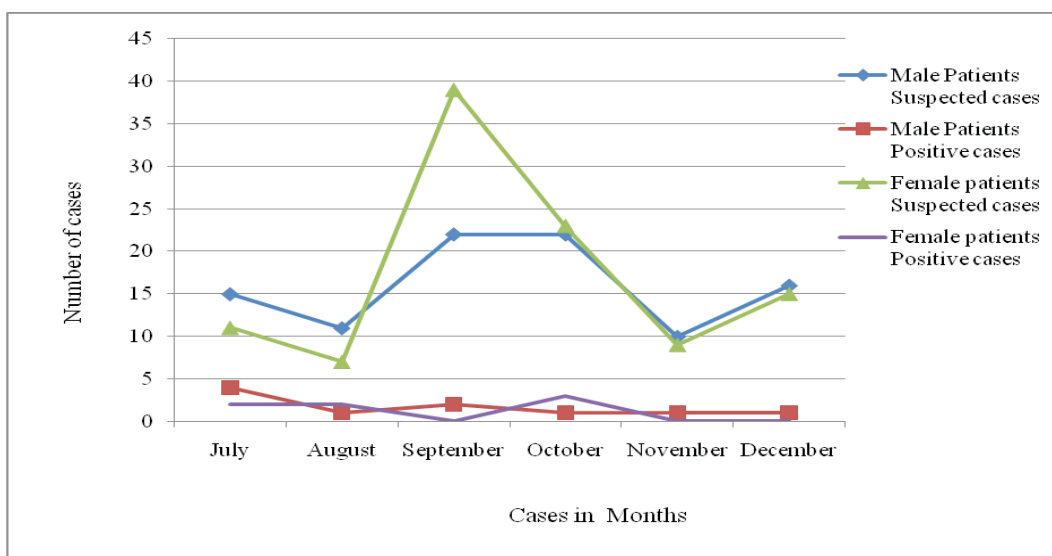


Figure 1. Month wise suspected cases and AFB positive male and female cases

Table 4. Association between different epidemiological variables and gender wise case detection

Sex	PTB among suspected cases			Test value
	AFB Positive	AFB Negative	Total	
Male	10	86	96	$X^2=0.452$ at $df = 1, p>0.05$ PPV= 10.4%
Female	8	96	104	
Total	18	182	200	

Note: Df = degree of freedom, PPV= Positive predictive value

## DISCUSSION

The study revealed that one; out of every ten suspected cases were AFB positive. Among all

smear positive cases, the male-female ratio was 5:4 which is in line with other similar study in Nepal and Pakistan<sup>9-12</sup> but somehow differ with a study conducted in Tribhuvan University teaching Hospital Kathmandu that showed male female ratio of PTB as 47:53.<sup>13</sup> Similarly our study is contrasts with a study in Afghanistan which showed 31.5% pulmonary tuberculosis occurred in males which was significantly lesser than female cases (68.5).<sup>14</sup> Age wise observation of the smear positivity in this study revealed that the higher numbers of positive cases were found in the age group 20 to 39 years. There is no significant difference in sex wise positivity rate in this age group. This finding is supported by other study reports from Afghanistan, Hong Kong and Nepal.<sup>14-17</sup> Study from Afghanistan showed the sex difference was greater in the



middle age groups including 15-44 years.<sup>12</sup> Study by Chan-Yeung et al. from Hong Kong reported that the sex difference in TB was greater in older than in younger which is somehow consistent with our study findings.<sup>15-16</sup> Study conducted, in Palpa and Kathmandu found the highest prevalence of TB among age group 20-30 years.<sup>16-17</sup> Higher prevalence of TB in the age group 20-39 is because people of these age groups are exposed to the outer environment as well as due to high work load and wide range of mobility.

Present study revealed that ward wise prevalence was highest (27.78%) in ward number four followed by ward number two (22.22%) and eight (16.67%). The proportion of male positive case detection was also higher (16.67%) compared to female positives(11.11%) in the community of ward number four and equal proportion (11.11%) in ward number one where the prevalence is in second highest on ranking. The wards where the high proportion of cases found are remote rural areas (>5 KM far from PHC) where the health education and health care facilities are inaccessible with compare to other wards (<5 Km from health facility) where the case detection proportion is low.

This study revealed that the prevalence of TB was found highest (one-third of total case detection) in July followed by August and September (22.22%). Among total 18 smear positive cases, the highest number of positive male cases (22.22%) found in the month of July which is double of female positive case (11.11%) in the same month. Similarly the highest female positive cases (16.67%) were detected in the month of October which is triple fold more than male positive cases (5.55%) in the same month. The reason of high prevalence of PTB in the month of August might be due to high incidence of cough and cold which may help in the transmission of PTB during coughing in the month due to seasonal change. Study carried out in other parts of Nepal showed the similar results.<sup>6-18</sup> Study from Hong Kong also showed the seasonal variation have significant role for occurring the pulmonary tuberculosis. The trough occurred in either January or February, while the peak occurred between May and August.<sup>19</sup> Similarly study conducted in four countries; Mongolia, Moldova, Zimbabwe and Uganda showed a similar trend of

case identification.<sup>19</sup> Excess proportion of cases among suspects in June and July, followed by a considerable decline to below average proportions from August through December in Mongolia. Lower than expected proportions were found in March in Moldova and Zimbabwe and in April in Uganda, while a higher than expected prevalence was recorded in September in Zimbabwe.<sup>20</sup>

## CONCLUSION

Males were found more likely to have pulmonary tuberculosis than females. Productive age group people were more vulnerable to PTB. There was no significant seasonal variation in PTB case identification though the suspected cases were high in September and October. Gender specific case identification and preventive measure targeting to the most productive age group population will eventually supports to reduce the risk of pulmonary Tuberculosis.

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## PREVALENCE OF TUBERCULOSIS AMONG HIV POSITIVE PATIENTS ATTENDING ICTC IN A TERTIARY CARE INSTITUTE IN AHMADABAD, A WESTERN CITY OF INDIA

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### ABSTRACT

**Introduction:** In India, tuberculosis is the most common opportunistic infection among HIV positive patients. This study estimates the prevalence of tuberculosis amongst HIV patients in Ahmadabad, Gujarat.

**Methodology:** The present study was conducted at Integrated Counseling and Testing Center for HIV at Sola civil hospital, a public sector tertiary care hospital in Ahmadabad for a twenty month period from January, 2009 to August, 2010. All the patients visiting the center during the study period were screened for HIV. All the patients who were diagnosed HIV positive were subjected for active search of tuberculosis; clinically, radiological as well as by histopathology and laboratory tests.

**Results:** Total 6846 patients were screened for HIV, out of which 167(2.44%) patients were tested HIV positive. Out of 167 HIV positive patients, 22 (13.17%) were diagnosed as cases of tuberculosis. Out of these 22 patients, 18(81.82%) had pulmonary tuberculosis while 4(18.18%) were extra-pulmonary tuberculosis patients. Amongst the four extra-pulmonary tuberculosis cases, one (25.00%) case was of tuberculous meningitis, one (25.00%) was of abdominal tuberculosis and two (50.00%) had tuberculous lymphatic swelling.

**Conclusion:** The prevalence of tuberculosis in HIV positive patients found in this study was 13.17%, which is substantially lower than that reported in previous studies. Appropriate management of these patients requires a strengthened mechanism of cross reference and inter sectoral co-ordination between the two diseases at all levels.

**Key words:** HIV/AIDS, Tuberculosis, Prevalence

### INTRODUCTION

Tuberculosis, though an ancient disease, continues to remain a major public health problem in much of the developing world even today. Worldwide it is the most prevalent infectious cause of human suffering and death.<sup>1</sup> The problem is now further complicated

by relentless spread of HIV and associated AIDS pandemic. HIV infection aggravates the progression to active disease in people infected with tuberculosis (TB). HIV infected individuals co-infected with TB bacilli have an annual risk of 5-15% of developing active TB.<sup>2</sup> In India, TB is the most common opportunistic infection among HIV sero-positive patients.<sup>3</sup> Currently in India 2.5 million people are infected with HIV of whom 40% are co-infected with TB.<sup>4,5</sup> HIV-TB co-infection represents a deadly combination. The co-infection is associated with various factors like malnutrition, unemployment, alcoholism, drug abuse, poverty, homelessness and illiteracy.<sup>6</sup>

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Further, appropriate management of patients with TB-HIV requires not only treating the TB and HIV alone but a strengthened mechanism of cross reference between the Anti-retroviral treatment (ART) centre and Directly Observed Treatment Short Course (DOTS) centre wherever indicated. If HIV prevalence in the community continues to increase, it could affect the TB control program, by decreasing cure rates and increasing mortality and recurrent TB.

So the present study was planned with the objective of estimating the prevalence of TB in HIV positive patients attending Integrated Counseling and Testing Center (ICTC) for HIV of a tertiary care public hospital at Ahmadabad, India.

## METHODOLOGY

Study design: This is a cross-sectional study.

Study setting: The study was conducted in ICTC centre of tertiary care public hospital in Sola, Ahmadabad, Gujarat, India.

Study period: January, 2009 to August, 2010

Sampling: All patients (n=6846) attending ICTC centre during the study period were included in the study.

Data collection: All patients attending ICTC in the study period were initially screened for HIV testing by various spot kits like Immunocomb, Tridot, SD HIV rapid test as per the National AIDS Control Programme (NACP) guidelines. Those who were found to be positive were rechecked by Enzyme Linked Immunosorbent Assay (ELISA) test before sending samples as a positive. An active search for TB disease was made in all HIV positive cases based on combined results of clinical, radiological, histo-pathological and laboratory investigations in accordance with protocol established by Revised National Tuberculosis Control Program (RNTCP).

Patient was diagnosed as a case of Pulmonary TB as per RNTCP protocol if

- 1) Either sputum smears (sputum acid-fast bacilli) positive 'OR'
- 2) Sputum smears negative but meeting all three of the following clinical criteria
  - a. Symptoms suggestive of TB
  - b. Chest X – Ray (Posterior-Anterior view) suggestive of TB

c. A positive anti – TB treatment response

Diagnosed of extra-pulmonary TB case as well determination of the focus of it was based on clinician's final judgment. This in turn was based on clinical examination as well as routine investigations like Hemoglobin (Hb), Total Lymphocyte counts (TLC), Differential Lymphocyte count (DLC), Erythrocyte Sedimentation Rate (ESR), urine (albumin, sugar and microscopic examination) performed in all cases. Other investigations like Fine Needle Aspiration Cytology (FNAC) of enlarged lymph nodes, abdominal ultrasonography (USG) and lumbar puncture were also performed on case to case basis as per the clinician's advice.

Ethics: The study was approved by the Institutional Ethical Committee (IEC) of Sola medical college. Informed consent was taken from all participants before testing. Pre-test counseling was also assured in all participants. Patients diagnosed with TB were started on Anti-TB Treatment (ATT) and were subjected to clinical and laboratory monitoring on a periodic basis and also at the conclusion of ATT from ethical point of view.

Data analysis: Data entry was done followed by data analysis using Epi Info 2007. Descriptive analysis with frequency distribution of patients for different variables was carried out.

## RESULTS

Total 6846 patients were screen for HIV during a study period of 20 months, out of this 167(2.44%) patients were found HIV positive. All 167 patients were screened for TB. Out of them (167), 22 (13.17%) were diagnosed TB positive and 145(86.83%) were TB negative (Table 1).

Table 1 shows that out of total 22 TB patients among HIV patients, 18(81.82%) had pulmonary TB while 4(18.18%) were extra-pulmonary TB patients. Out of 18 pulmonary TB, 12(66.67%) were detected by sputum examination with Zeil Nelson (ZN) staining and 6(33.33%) were detected by X-Ray chest findings. Amongst four extra-pulmonary TB cases, one (25.00%) case was of TB meningitis, one (25.00%) was of abdominal TB and two (50.00%) were of TB lymphatic swelling.

**Table 1.** Distribution of tuberculosis among HIV positive patients

Amongst HIV positive patients(n=167)		Total HIV positive	Total patients screened	
Tuberculosis positive	Tuberculosis negative			
22(13.17%)	145(86.83%)	167(2.44%)	6846(100%)	
Amongst Tuberculosis positive patients (n=22)				
Pulmonary tuberculosis		Extra-pulmonary tuberculosis		
18(81.82%)		4(18.18%)		
Amongst pulmonary tuberculosis patients (n=18)		Amongst extra-pulmonary tuberculosis patients (n=4)		
Diagnosed by Ziehl-Neelsen stain	Diagnosed by chest X-ray	Tuberculosis meningitis	Abdominal tuberculosis	Tuberculous lymphatic swelling
12(66.67%)	6(33.33%)	1(25.00%)	1(25.00%)	2(50.00%)

Out of total 167 HIV positive patients, 108(64.67%) were males and 59(35.33%) were females. Maximum number of HIV positive patients 69(41.32%) were from 25 to 34 years of age (43(25.75%) males and 26(15.57%) females). After that 62(37.13%) of patients were from 35 to 49 years of age (41(24.55%) males and 21(12.57%) females).

Our study shows maximum number of TB patients 9(40.91%) among HIV positives were also from 25 to 34 years of age group. After that 8(36.36%) of patients were from age group of 35 to 49 years. Only 2(9.09%) of patients were less than 14 years of age.

Among TB patients, 16(72.73%) patients were males and 6(27.27%) were females.

## DISCUSSION

The prevalence of TB amongst HIV positive patients at ICTC was 13.17% in present study. Another Madras bases prospective study by Solomon S et al in 1995 (n=1430) on trends on HIV infection in Pulmonary TB showed the co-infection prevalence to be 3.4%.<sup>7</sup> Ghate MV et al from Pune in his cross-sectional studies conducted consecutively for three years have shown the prevalence of TB in HIV infection to be 11.8%, 9.94% and 7.4% in the year 1997, 1998, 1999 respectively (n=3574).<sup>8</sup> While in contrast to this one Lucknow based cross-sectional study by Sircar AR et al in 1998 (n=74) showed the same prevalence to be quite high, that is 54.8%.<sup>9</sup> Kumar P et al, 2002 from Delhi showed that the prevalence of Acid Fast Bacilli (AFB) positive sputum amongst HIV patients is 21.4%, while

the prevalence of extra pulmonary TB infection is almost double that is 45.6% (n=306).<sup>10</sup> Similarly the prevalence of Multi drug resistant (MDR) TB amongst HIV infected persons was found to be 4.42% by a Chennai based investigator in 2002 in a cross-sectional study conducted on 1000 patients.<sup>11</sup> A case control study (n=1009) conducted in Mumbai by Hira SK et al (n=1009) have shown the prevalence of TB amongst HIV cases is 25.4%.<sup>12</sup> Where as a Calcutta based cross-sectional study have shown the same prevalence of TB among HIV patients to be 27.7%.<sup>13</sup> Likewise a study on Bone TB prevalence amongst HIV patients have found the prevalence of the same to be around 40% (n=140).<sup>14</sup> Mahajan A et al from Jammu has shown the prevalence of HIV-TB co-infection of 16.52%.<sup>15</sup>

Thus it is evident from above evidences that there is wide regional variation in the prevalence of HIV-TB co-infections in India and hence findings of one region cannot be extrapolated to other regions without a proper study. Though difference in the strengths of study designs, sample size and study period (prospective studies superior than cross-sectional) as well as center to center diagnostic capabilities especially for extra pulmonary TB and lack of standard to compare for the same might also be responsible for these huge variations.

There are also many studies from out of India showing different rate of HIV prevalence, indicating even a huge inter country variation in addition to the intra country variation for the same. Like a review study from Netherlands in 90's (n=13269) has shown the prevalence of HIV amongst TB patients to be around 4%<sup>16</sup>, while a study from

Ukraine has shown the prevalence of co-infection to be 6.3% and 10.1% respectively in 2002 (n=567) and 2004 (n=968) respectively<sup>17</sup>, where as a hospital based review study from Nigeria has shown the same prevalence to be around 28.12% (n=777)<sup>18</sup>, which is again in contrast to another Uganda based retrospective evaluation (n=6305) of 5%<sup>19</sup>, and Atlanta, USA based cross-sectional evaluation (n=272) of 1% sero-prevalence among TB patients.<sup>20</sup>

To promote early diagnosis and treatment of TB in HIV infected individuals and vice versa, at the national level, there is a concerted effort to achieve coordination between the designated microscopy centre (DMC) of the RNTCP and the ICTC of the HIV/AIDS control program not only to improve the outcome of HIV-infected TB patients but also to control the burden of tuberculosis in India<sup>21</sup>. As a part of this all ICTC clients with suggestive symptoms are referred by the counselor to the nearest microscopy centre for investigations to rule out TB.<sup>21</sup> In 2007, approximately 5% of all diagnosed TB cases in India came from ICTCs.<sup>21</sup>

Our study shows pulmonary involvement in 81.82% of cases which is almost equal to results of Deivanayagam et al, 2001 and Ahmad and Shameem, 2005 which shows pulmonary involvement of about 75% of all HIV infected patients with TB.<sup>22, 23</sup> TB-HIV co-infection is already a well recognized public health problem particularly in developing countries.<sup>1,9,10</sup> HIV infection is the most potent factor in transforming latent or recently acquired TB infection to active clinical disease.<sup>24, 25</sup>

Extra-pulmonary TB is the commonest cause of pyrexia of unknown origin (PUO) among HIV positive individuals in developing countries and is more common among people with advanced HIV disease.<sup>26,27</sup> The most frequent extra-pulmonary form of TB is involvement of the lymph nodes with cervical region being the commonest.<sup>28</sup> The other forms of extra-pulmonary TB include pleural effusion, pericardial effusion, abdominal TB, TB meningitis and abdominal TB.<sup>21</sup> In current study 4 (18.18%) were extra-pulmonary TB patients with two of them having tuberculous lymphatic swelling, one having abdominal TB and one case of TB meningitis. Another study by Mansoori et al showed 80.9% cases of smear-positive pulmonary

TB, 10.9% of smear-negative pulmonary TB; and 8.2% of extra-pulmonary TB which consisted of 3 cases of TB lymphadenitis, one pleural TB case, one case of TB meningitis, and one liver TB case.<sup>29</sup>

Patients with HIV co-infection may not have typical radiographic features of pulmonary tuberculosis on chest X-ray and it may be normal in 5-10% of individuals.<sup>30</sup> While patients with higher CD4 cells (>350 cells/mm<sup>3</sup>) have radiographic abnormalities similar to their HIV negative counterparts, patients with immunosuppression often have minimal or atypical findings which includes diffuse pulmonary infiltrates/opacities dominantly and uncommonly cavitation.<sup>31</sup> Miliary pattern, mediastinal adenopathy and pleural effusion are also more common.<sup>30</sup> In current study out of total diagnoses pulmonary TB cases 33.33% were diagnosed by chest x-ray.

Our study shows that out of total HIV positive patients, 35.33% were females, which is almost equal to National AIDS Control Organization (NACO) report 2007 showing that among all HIV positive patients 31.2% are females.<sup>32</sup> Yadav DK et al showed the proportion of females amongst the HIV positives of 24.8%.<sup>33</sup>

Our study reveal that maximum number of HIV positive patients 69(41.32%) were from 25 to 34 years of age. Yadav DK et al revealed that majority of HIV positive subjects are in the age group of 30-39 years (48.8%).<sup>33</sup>

Our study shows that maximum number (40.90%) of TB-HIV co-infected positive patients were from 25 to 34 years of age group. After that 36.36% of patients were from age group of 35 to 49 years. These results are almost equal to Bernard J Ngowi et al's findings which shows the same prevalence as 45.0% and 30.0% in the age group of 25 to 34 years and 35 to 49 years respectively.<sup>34</sup> Yadav DK et al revealed that 60% of TB/HIV co-infected belonged to the age group (31-40) years, while 35.7% of subjects was belonged to age group (21-30) years.<sup>33</sup> Mansoori D et al revealed that 64% of TB/HIV infected patients were 20-40 years old and 36% were 41 years old or more.<sup>29</sup>

Limitation:

It is possible that some under diagnosis, especially of extra-pulmonary TB as well as sub clinical

infections did occur, as our diagnostic methods were restricted to sputum smears, radiographs, clinical judgment and routine laboratory tests. Other investigations like USG, FNAC was done only in symptom suggestive patients based on clinician's advice.

## CONCLUSION

In this study 22(13.17%) subjects were patients with HIV-TB dual disease, most of whom were pulmonary TB cases. This prevalence is substantially lower than that reported in previous studies indicating regional variations in the prevalence of the same.

Further appropriate management of these patients requires a strengthened mechanism of cross reference and inter sectoral co-ordination between the two diseases at all levels which requires further operational research. One of the programmatic limitations encountered in this is the lack of investigations for extra-pulmonary TB at peripheral health facilities.

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## RISK FACTORS FOR DRUG INDUCED HEPATITIS UNDER DOTS PROGRAMME IN GENERAL POPULATION

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### ABSTRACT

**Background:** Short course chemotherapy containing rifampicin and isoniazid in combination has proved to be highly effective under DOTS regimens in the treatment of tuberculosis, but one of its adverse effects is hepatotoxicity. Little however has been published regarding drug induced hepatitis (DH) under general programme conditions. In this study, we aimed to determine the prevalence of drug induced hepatitis and the risk factors associated with the development of hepatitis over a period of 5 years.

**Methodology:** This was a prospective study done from 2007 to 2011 in a tertiary care hospital. A total of 116 patients were included in the study that presented with hepatitis due to short course chemotherapy and were being treated under various categories of drug regimens. Forty cases were being followed up and other 76 were seen at the hospital for the first time after the development of hepatitis. The diagnostic criteria's for drug-induced hepatitis were made according to the ATS criteria's. Various risk factors were analyzed for the development of DH.

**Results:** The prevalence of DH in the present study was 3.6%. It was observed that DH patients were older and their serum albumin levels were lower. Regular alcohol intake, more extensive disease radiologically and female gender were observed to be independent risk factors for the development of DH. No other risk factors analyzed had any significant association with DH.

**Conclusion:** Of the various risk factors analyzed, advanced age, hypoalbuminaemia, regular alcohol intake and advanced nature of the disease were independent risk factors for the development of DH. The risk of hepatitis in the presence of one or more of these risk factors may be increased.

**Key words:** Chemotherapy, DOTS, Drug Induced Hepatotoxicity, Tuberculosis.

### INTRODUCTION

Tuberculosis (TB) causes a great deal of ill health in the populations of most low-income countries, and due to this world adopted DOTS strategy for TB control though the national TB control programs

worldwide and is making good progress. In India, DOTS strategy has been implemented since 1996 and has already reduced the number of deaths. Short course chemotherapy containing rifampicin and isoniazid in combination with ethambutol and pyrazinamide has proved to be highly effective in the treatment of tuberculosis<sup>1</sup>, but one of its adverse effects is hepatotoxicity. The reported incidence of hepatotoxicity in controlled trials of antituberculosis chemotherapy which included INH, RMP and PZA ranged from 0.6 to 3%.<sup>2-4</sup> Little, however, has been published regarding TB drug-induced hepatitis (DH) under general programme conditions.

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However, if serious side-effects do occur and treatment with one of the three drugs must be finally terminated, the patient no longer receives the best treatment available and might be at a higher risk of treatment failure and possibility of development of drug resistance. It has been very important to draw attentions of all health workers towards side effects of anti-tuberculosis drugs since side effects can be harmful to the patients. Hepatotoxicity is one of the important side-effects of anti-TB drugs especially during the initial intensive period, and monitoring is crucial during this period, but may be costly. Awareness of the risk groups may decrease the cost as well as the incidence of serious drug related adverse effects. In this study, we aimed to determine the prevalence of drug induced hepatitis and the risk factors associated with the development of hepatitis over a period of 5 years.

## METHODOLOGY

This was a prospective study done from 2007 to 2011 in a tertiary level care KLES Dr. Prabhakar Kore Hospital and MRC at Belgaum, Karnataka, India. All the patients were being treated under various categories of DOTS regimens. The patients who were registered under Category I, II and III were included in study. Thus, a total of 3221 patients who were registered under these regimens, during the above period were included in this study. A total of 116 patients who presented with hepatitis due to the short course anti-tuberculous therapy to the department of Pulmonary Medicine were included in the analysis. Forty cases were being followed up and the other 76 were seen at the hospital for the first time after the development of hepatitis. All these 116 cases have been analyzed in detail.

### Diagnosis of Drug induced Hepatitis (DH):

The diagnostic criteria for drug-induced hepatitis were as follows<sup>5</sup>: (1) A rise of five times the upper limit of normal levels (50 IU/L) of serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT); (2) A rise in the level of serum total bilirubin >1.5 mg/dl; (3) Any increase in AST and/or ALT above pre-treatment levels together with anorexia, nausea, vomiting, and jaundice; (4) Absence of serologic evidence of infection with hepatitis virus A, B, C, or E. Viral hepatitis markers (HBsAg, IgM anti-HAV, IgM anti-HBc, and anti-HCV second generation antibodies) were analysed using ELISA immunoassay kits. The

presence of any one of the first three criteria's along with absence of viral hepatitis was considered to be having drug-induced hepatitis (DH). Patients with associated chronic illnesses such as cirrhosis of the liver, chronic hepatitis, acute viral hepatitis, gastro-intestinal, renal or cardiac diseases were excluded.

### Drug Regimens:

The drug regimens used were as follows:

Category 1 (2R<sub>3</sub>H<sub>3</sub>E<sub>3</sub>Z<sub>3</sub>/4R<sub>3</sub>H<sub>3</sub>): rifampicin, isoniazid, ethambutol and pyrazinamide given thrice weekly for two months followed by rifampicin plus isoniazid thrice weekly for four months.

Category 2 (2S3R3H3E3Z3/1R3H3E3Z3/5R3H3): streptomycin, rifampicin, isoniazid, ethambutol and pyrazinamide given thrice weekly for two months followed by four drugs for another 1 month of intensive phase and then rifampicin and isoniazid given thrice weekly daily for five months.

Category 3 (2R<sub>3</sub>H<sub>3</sub>Z<sub>3</sub>/4R3H3): same as regimen 1 except for deletion of ethambutol. The regimen is given for total duration of 6 months.

Category 4: Drug resistant cases. Here the second line drugs were given according to the AFB culture and sensitivity testing. Hence the drug regimen was individualized to each patient.

Category 4 patients were neither considered for the final analysis, nor for the calculation of DH. Thus, only the first three regimens were studied for the DH.

### Drug Dosages:

The drug dosages were calculated in relation to the weight of the patients as follows:

- (1) Streptomycin: 0.75 gm IM (< 50 years) and 0.50 gm (> 50 years)
- (2) Rifampicin: body weight < - 450 mg/day; > 50 kg - 600 mg.
- (3) Isoniazid: 600 mg (10 – 15mg/kg).
- (4) Ethambutol: 1200 mg (30 mg/kg).
- (5) Pyrazinamide: 1500 mg (30 – 35mg/kg).

**Study Design:** Data on patient demographics, co-morbidity, use of concomitant medications, alcohol consumption, body weight, baseline transaminases/bilirubin and treatment regimen were recorded for all the patients. All the baseline investigations were performed including HIV status. In addition to the patients' data and treatment data, the following information on risk factors were analysed: alcohol abuse (>40 g·day<sup>-1</sup>); i.v. drug abuse; history of hepatitis; hepatic damage at admission (liver enzymes at admission  $\geq 2$  times normal values); history of diabetes mellitus; HIV infection and concomitant therapy with other hepatotoxic drugs (Table 1). The incidence of DH was determined, and the patient and treatment characteristics of those who developed DH were compared with the rest of the cohort. The clinical course and treatment outcome of the patients with DH were also studied. All patients had baseline serum transaminase and bilirubin levels measured prior to starting treatment, and were routinely advised to report immediately should they experience symptoms of hepatitis such as nausea, vomiting or abdominal pain. Monitoring of serum transaminase/ bilirubin levels was carried out in high-risk patients (e.g., history of liver disease or alcohol abuse), or if symptoms or signs suggestive of hepatitis occurred. Chest radiography was performed in all the patients with DH to know the extent of the disease radiologically. It was our operating policy that if a patient developed hepatitis according to the above criteria, TB treatment would be temporarily stopped, even in the absence of symptoms. All drugs were stopped and liver function tests were conducted twice a week. Once liver functions were returned to normal, the drug regime was restarted with all drugs at the same time and full-doses. If hepatotoxicity recurred, the drugs were reintroduced in stages as follows: first EMB at the maximum dosage of 1500 mg and INH at 100 mg. The INH dosage was increased by 100 mg/day to the maximum dosage of 300 mg on the third day. RIF was re-introduced from the fourth day starting at 150 mg and increasing by 150mg on alternate days until the maximum dose of 600 mg was achieved. Once RIF had been re-introduced to its maximum dosages, PZA was started at 500 mg and the dosage increased by 500 mg on alternate days until the maximum dosage of 1500 mg was achieved.

The risk factors for the development of DH were analyzed in details: age, gender, past history of

anti-tuberculosis treatment, extensive nature of radiological disease, co-morbid disorders and drug resistance for the development and recurrence of hepatotoxicity. The INH acetylation status was not analysed in this study as we do not have the facility for the same. Ethical clearance was taken from the institutional ethical committee.

**Data Analysis:** Statistical analysis was made using computer software (SPSS version 13.0, SPSS Inc. Chicago). Data were analyzed by chi-square ( $\chi^2$ ) test and logistic regression analysis. Data were expressed as "mean (standard deviation; SD)", minimum-maximum and percent (%) where appropriate.  $p < 0.05$  was considered statistically significant. Continuous variables (ALT and AST) that failed in the assumption of normality and homogeneity of variance were compared across the groups using the Mann-Whitney test. Binary logistic regression was used to calculate the adjusted odds ratio for the significant risk factors of DH. Logistic regression univariate analysis was performed to analyze the risk factors associated with DH. Furthermore, to remove the confounding variables, we did multivariate Logistic regression analysis to assess the role of independent risk factors for development of DH.

## RESULTS

The risk of development of drug induced hepatitis (DH) in the present study was 3.6% (116 patients out of total cohort of 3221 patients). We have analyzed these 116 patients who developed DH in detail. The detail baseline characteristics of the patients who developed DH are shown in Table 1. The mean age was  $47 \pm 7.2$  years. Majority of the patients were above the age of 60 years (39.6%). Males composed of 63.1% of patients. The average duration of development of DH was 20 days after starting anti-tubercular therapy and lasted for average of 14 days. Hepatotoxicity was observed to develop for once in 81.9% ( $n = 95$ ) of patients while it recurred for more than once in 18.1% ( $n = 21$ ) patients. Majority of the patients had pulmonary tuberculosis (54.3%), followed by pleural tuberculosis (17.3%). Most of the patients had associated co-morbid conditions, with the commonest being COPD (41.4%), followed by diabetes mellitus (21.6%). Forty nine patients (42.2%) had history of alcohol consumption, with more than half being drinking almost on daily basis.

RNTCP Category I patients contributed to 65.5% of the patients, while another 10.3% were under Category II, and rest 24.1% were under Category III regimen. It was observed that the prevalence of DH was almost the same in all the categories of the patients (Table 2).

The rise in ALT and AST was almost 5 times the upper limit of normal (ULN), while the bilirubin was raised to > 2.0 mg/dl, with some patients being raised up to 10mg/dl (Table 3). There were some cases where ALT and AST were raised to 3 times ULN along with symptoms of hepatitis, and we had to stop the therapy.

Table 1. Patient's characteristics at Baseline (N =116 who developed DH)		
Age (Years)	No.	(%)
Mean (Range)		
< 20 years	12	10.3
20– 40 years	28	24.1
40 – 60 years	30	25.8
> 60 years	46	39.6
Males	65	56.1
Females	51	43.9
<b>Site of disease</b>		
Pulmonary TB	63	54.3
Pleural TB	20	17.2
Larynx TB	3	2.6
Lymph node TB	12	10.3
Abdominal TB	10	8.6
CNS TB	6	5.2
Bone/Joints TB	2	1.7
<b>Comorbid conditions</b>		
Diabetes mellitus	25	21.6
COPD	48	41.4
Cor pulmonale	10	8.6
Chronic renal failure	6	5.2
HbsAg (+ve)	2	1.7
Epilepsy	3	2.6
History of alcohol consumption	49	42.2
History of malignant disease	3	2.6
Presence of extensive disease	41	35.3
<b>Category of patients</b>		
Category –I	76	65.5
Category –II	12	10.3
Category –III	28	24.1
<b>Total cases</b>	<b>116</b>	<b>100</b>

**Table2.** Drug induced hepatitis (DH) among different categories

Category Regimen	Total No. of Patients	DH Patients	%	p value
Category I	2083	83	3.6	NS
Category II	336	12	3.6	NS
Category III	802	28	3.5	NS

p value is calculated by comparing category I with II and III, and category II with III.

**Table 3.** Pre-treatment and post-treatment liver function tests in 116 DH patients (Data presented of all 116 cases that had developed DH)

	Pretreatment (Mean ±SD)	Post-treatment [median (range)]
Ser Bilirubin, mg/dl	0.5 (0.1)	2.3 (0.7 -11.0)
AST, IU/L	50 (21)	346 (71 -1112)
ALT, IU/L	41 (27)	415 (45 -1421)
Ser Alkaline phosphatase	78 (70)	319 (219 -758)
Ser proteins, gm/dl	6.8 (1.2)	6.9 (5.4 – 9.1)
Ser albumin, gm/dl	2.0 (0.8)	2.2 (1.9 – 5.2)
Ser globulin, gm/dl	3.5 (0.6)	3.6 (1.8 – 6.6)

**Risk factors for development of DH:** Elderly patients (>60 years) were observed to be at higher risk of developing DH. It was observed that DH was lower among younger age group (<20 years) (10.3%), while it was observed to be present in 39.5% of patients > 60 years of age group. Hepatotoxicity was identified in 9.2% of patients with limited disease while in 35.3% of patients had radiological extensive disease. The development of hepatotoxicity was significantly more common in patients with extensive disease (p= 0.003; Table 3). Co-morbid disorder was evident in 77 cases in the present study. The development of hepatotoxicity was significantly more common in patients with associated co-morbid conditions (Table 1). Past history of anti-tuberculosis treatment was present in 10.3% (n=12) of the cases. Hepatotoxicity was identified in 19.1% of these cases. Alcohol consumption was common especially among the younger age group, and these patients developed DH in 42.2% of the cases. It was also found to be an independent risk factor for the development of DH. About 12 patients had previous history of hepatitis, this may be viral hepatitis with jaundice, and these patients were at higher risk of development of DH

following anti-TB therapy. A lower serum albumin level was also found to be associated with DH. The mean serum albumin level in patients with DH was 2.0gm/dl.

A total of 21 patients developed recurrence of DH. It was observed that the factors that contributed for the development of DH were: previous hepatitis episode, previous anti-TB treatment, age > 60 years, extensive disease on radiology, hypoalbuminaemia and alcohol consumption. Past history of anti-tuberculosis treatment was the only risk factor determined to be significantly associated with recurrence ( $p= 0.027$ ).

On univariate analysis, the factors that were significantly associated with DH were prior history of hepatitis, age > 60 years, female sex, alcohol consumption, previous anti-TB therapy, hypoalbuminaemia, extensive nature of disease and diabetes mellitus (Table 4). On multivariate analysis, the significant risk factors that were associated with DH were female sex, prior history of hepatitis, alcohol consumption, hypoalbuminaemia, age > 60 years and extensive nature of disease radiologically (Table 5).

**Table 4.** Univariate analysis of Risk factors for DH (N =116)

	OR	95% CI	p value
History of hepatitis	2.5	1.4 – 3.6	(0.001)
Age > 60 years	2.0	3 – 4.3	(0.005)
Female sex	2.1	0.7 – 4.3	(0.002)
HIV infection	1.9	0.5–7.2	(0.45)
Alcohol abuse	0.9	0.6–3.7	(0.05)
Hepatic disease at admission	1.12	0.4–2.8	(0.70)
Concomitant hepatotoxic drugs	1.22	0.7 – 3.1	(0.15)
Hypoalbuminemia	2.1	1.4 -3.7	(0.005)
Previous anti-TB therapy	2.4	1.1 – 3.6	(0.01)
Extensive disease	2.7	2.3 -4.7	(0.003)
Diabetes mellitus	1.8	0.8 – 2.5	(0.05)
COPD	2.3	1.1 – 3.3	(0.89)

**Table 5.** Multivariate analysis of Risk factors for DH (N =116)

	OR	95% CI	Likelihood p value
<b>Independent Variables associated with DH</b>			
Age > 60 years	3.1	1.6 – 7.6	7.5 0.002
Female gender	1.6	1.0 – 2.5	3.5 0.03
Alcohol abuse	2.2	1.9 – 5.3	4.6 0.005
Hypoalbuminemia	3.2	1.4 -5.4	6.6 0.002
Extensive disease	2.3	2.1 – 4.9	4.3 0.002
History of hepatitis	1.5	1.6 - 4.3	4.2 0.01
<b>Dependent Variables associated with DH</b>			
Abnormal baseline transaminases/ bilirubin	1.2	0.2 – 1.5	1.4 0.27
Previous anti-TB therapy	1.3	0.3 – 2.1	0.3 0.56
Diabetes mellitus	1.1	0.6 – 2.3	0.4 0.35

**Management of Hepatotoxicity:** Anti-tuberculosis treatment was continued at full dosage after the normalization of liver enzyme levels in 82.7% ( $n= 96$ ) of patients with hepatotoxicity. In recurrent hepatotoxicity a step-by-step anti-tuberculosis treatment was re-started and patients could tolerate all the drugs successfully. Thus, it was possible to administer the treatment regimen to all the patients without modification of WHO treatment guidelines.

## DISCUSSION

The presence of drug induced hepatotoxicity (DH) in the present study was observed to be 3.6%. the prevalence of DH was observed to be same among all the three different categories. The drug resistant cases that were on category IV were not included in the study, and hence they were not analyzed for DH. The frequency of DH, which is the most important side effects of tuberculosis treatment, varies in different countries varies ranging from 1% to 10%. Depending on factors such as race, socio-economical condition and geographical location, the frequency was determined to be highest in developing countries (8% - 10%) while lower in

Western countries being < 1% in US, 4% in UK, and 3.3% in Barcelona<sup>6</sup>. Meaningful comparison of the incidences of reported hepatotoxicity across different treatment centres is often not possible, as hepatitis has not been consistently defined in the literature. Definitions have ranged from asymptomatic elevation of transaminases of 2 X ULN, to symptomatic, jaundiced individuals with AST >150 U/L<sup>7</sup>. The relatively higher incidence of hepatotoxicity in the developing countries has been attributed to various factors such as older age, higher alcohol intake, malnutrition, intestinal parasitism, past history of jaundice, chronic liver disease, indiscriminate use of drugs, and viral hepatitis<sup>8</sup>. There is no consensus as to which one of these factors, whether alone or in combination, is involved in the development of drug-induced hepatitis and whether anyone could be used as markers to identify patients at higher risk.

The various reported risk factors for hepatotoxicity include older age, child age, female sex, poor nutritional status, high alcohol intake, pre-existing liver disease, hepatitis B and C infections, extensive disease, hypoalbuminaemia and acetylator status. In all disease groups, close follow-up is required during treatment with periodical clinical controls and laboratory tests.<sup>9</sup> In one meta-analysis, the presence of rifampicin in a multidrug treatment regimen was reported to increase the incidence of significant hepatotoxicity among adults from 1.6% to 2.55%.<sup>10</sup> The pyrazinamide has also been demonstrated to contribute to increased incidence or severity of hepatotoxicity.<sup>11</sup>

Increasing age group was observed to be a significant risk factor for development of DH. Various other studies also have found similar prevalence. Babalik et al<sup>12</sup> has observed that age > 40 years were at higher risk for the development of DH, while another study from India has also observed higher prevalence of DH in > 60 years of age group. The higher incidence of hepatotoxicity in older age may be secondary to increased prevalence of co-morbid conditions as well as use of related additional drugs in this age group. Female gender has been also found to have higher prevalence of DH. Other studies have also reported a female preponderance amongst those developing hepatitis although the exact reason is not known.<sup>14</sup>

On multivariate analysis, other risk factors that were independently associated with significant DH in the present study were alcohol abuse, extensive nature of pulmonary tuberculosis disease, and hypoalbuminaemia. Malnourished children also have been observed to have threefold increased incidence of DH in one study<sup>15</sup>, while in another study<sup>4</sup> it was found that patients with pretreatment hypoalbuminaemia had a twofold higher risk of developing DH. Other measures of malnutrition, such as BMI and triceps skin fold thickness, were not predictors of DH. It appears that under-nutrition as identified by hypoalbuminaemia may in itself be a risk factor for drug-induced liver injury. The possibility that hypoalbuminaemia was caused partly by the development of hepatitis itself cannot be ruled out. It was also observed that high alcohol intake and advanced tuberculosis were associated with DH.<sup>5,16,17</sup> Moderately/far advanced pulmonary TB was an independent predictor of DH in many studies.<sup>5,13</sup> High alcohol intake was recorded in 20% of the cases, indicating that consumers of high alcohol are more prone to develop hepatotoxicity. The disease extent was also a significant risk factor for the development of hepatitis. In patients with advanced disease, multiple factors may play a role in developing DH. This includes underlying nutritional status, hypoalbuminaemia, alcohol abuse and long standing nature of disease which will lead to undernourishment of an individual.

The addition of pyrazinamide to the regimen increases the risk of DH.<sup>18</sup> But such incidence was not observed in the present study. Another factor that may be responsible for DH is the acetylation status of the patients. But the reported data show no consensus, both fast and slow acetylators have been reported to be more prone to developing hepatotoxicity on short course chemotherapy<sup>19</sup>. Pande et al<sup>13</sup> observed that DH to be more frequent among slow acetylators as compared to the control group. We could not assess the acetylation status of an individual and but one should keep acetylation factor in mind. Certain immunogenetic risk factors have also been studied for DH and it was observed that absence of HLA-DQA1\*0102, and presence of HLA-DQB1\*0201 were independent risk factors for DH.<sup>5</sup>

All patients who developed viral hepatitis during anti-tuberculosis treatment were excluded in this study,

although the possibility that a few of them had viral hepatitis that was not detected by the serological tests used cannot be excluded. Serological markers were evaluated only for hepatitis A, B, and C virus. Kumar et al<sup>20</sup> observed that the reported high incidence of drug-induced hepatitis in developing countries was, to a significant extent, attributable to these viral infections.

According to recommendations, if the diagnosis is drug-induced hepatitis, the anti-tuberculosis drugs should be stopped and the drugs must be withheld until the normalization of the liver function tests<sup>21</sup>. ATS recommends initiation of the new treatment regime following hepatotoxicity provided that ALT levels are below the two fold of upper normal limits. In this study, treatment was re-initiated only after normalization of liver enzymes. There are different opinions about initiation of treatment after normalized liver functions tests. ATS recommends initiation of the therapy with rifampicin monotherapy or combined E + R treatment with addition of H to the treatment regime after 3-7 days if no elevation is evident in ALT levels and addition of Z after 3-7 days with control of ALT levels. WHO recommended re-introduction of all the drugs at once when drug-induced hepatitis was resolved with discontinuation of the latest drug added in case of symptom recurrence or abnormality in liver function tests.<sup>21</sup> In the present study, we started the full drug dosages after the normalization of the enzyme values in all the cases and 21 (18.1%) of 116 cases had recurrent hepatotoxicity. Another study<sup>12</sup> had observed the prevalence of 21.7% risk of DH during reintroduction of the drugs. In recurrent hepatotoxicity, a step-by-step treatment approach was re-started in re-initiation of the drugs. The risk factor associated with recurrent hepatotoxicity was past ant-TB history. Tahaoglu et al<sup>22</sup> compared the efficacy of two different re-treatment protocols including reintroduction of full-dose regime with pyrazinamide and gradual reintroduction of a regimen without pyrazinamide in recurrent hepatotoxicity tuberculosis patients. They reported higher recurrence rate of hepatotoxicity in the retreatment of tuberculosis with a full-dose regimen including pyrazinamide.

Management of active tuberculosis includes the initiation and completion of the anti-TB therapy, and also interferences of side effects related to anti-TB drugs. The study showed that drug induced is a

frequent side effect of anti-TB therapy under DOTS therapy. DH could considerably impact the anti-TB treatment, potentially leading to unsuccessful treatment outcomes and the prolongation of intensive treatment phase. Early diagnosis and identification of the risk factors for DH is important to prevent hepatitis induced mortality. Therefore, more research and efforts are warranted in order to enhance the diagnosis and the prevention of DH.

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## PREVALENCE AND CD4 CELL COUNT PATTERN OF TB CO-INFECTION AMONG HIV INFECTED INDIVIDUALS IN NEPAL

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### ABSTRACT

**Background:** Mycobacterium tuberculosis (TB) and Human Immunodeficiency Virus (HIV) infections are two major public health problems in many parts of the world, particularly in developing countries like Nepal. The objective of the study is to find out prevalence and clinical presentation of the TB co-infection among HIV infected individuals and pattern of CD4 cell count in relation to types of TB and response of ART.

**Methodology:** This is a cross-sectional study carried out in three VCT clinics from Dharan and Kathmandu from April 2010 to March 2011. The appropriate samples, 313 HIV individuals were taken as study sample.

**Results:** The study revealed that more than 36% of individuals were co-infected with TB. Among them, nearly 65% had pulmonary TB, more than one-fourth had gland TB. There is significant association of TB co-infection among male compared to females ( $P=0.021$ ). Fever, weight loss and cough were found to have significant symptoms associated with TB-HIV co-infection. The average CD4 count among TB co-infected population was significantly less compared to uninfected ones just before starting ART ( $P=0.022$ ) and even after six months ( $P=0.001$ ). After one year of ART continuation, there was no significant association on average CD4 count among the two groups. But then, the mean CD4 count became more in TB co-infected individuals compared to those who had no TB co-infection.

**Conclusion:** TB-HIV co-infection is an emerging medical issue in Nepal. More than one third of HIV patients are co-infected with TB. Consideration of TB need to be made while caring patients with HIV infection and vice versa. ART plays very important role in increasing CD<sub>4</sub> cell count among TB-HIV co-infected patients.

**Key words:** HIV, TB co-infection, CD4 cell count, Clinical features, ART

### INTRODUCTION

The United Nations Joint Programme on HIV/AIDS (UNAIDS, 2009) report estimated that 33.4 million people are living with Human Immunodeficiency

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Virus (HIV) in worldwide, and one third of them are co-infected with tuberculosis (TB). HIV infection increases susceptibility to TB and is the most potent factor in transferring latent or recently acquired TB infection to active clinical diseases. In addition, TB in high HIV prevalence populations is a leading cause of morbidity and mortality. TB patients have been suggested to be an important population for finding of HIV infections. Therefore, prevention and control of co-infection is vital to reduce the epidemic of TB and HIV/AIDS.<sup>1</sup>

An estimated 2 million deaths have been attributed annually to HIV/AIDS, with approximately 250,000

pediatric deaths.<sup>2</sup> In infants and young children, immune system immaturity and high viral loads lead to a high risk of rapid disease progression.<sup>3</sup>

Since the detection of the first AIDS case in 1988, the HIV epidemic in Nepal has evolved from a low prevalence to concentrated epidemic. As of 2009, national estimates indicate that approximately 63,528 adults and children are infected with the HIV virus in Nepal, with an estimated prevalence of about 0.39% in the adult population.<sup>4</sup>

*Mycobacterium tuberculosis* and human immune deficiency virus infections are two major public health problems in many parts of the world, particularly in many developing countries.<sup>1</sup> Co-infection with HIV may worsen the course and complicate the diagnosis and management of TB. Overall, HIV-infected patients have 60% higher risk of acquiring TB in comparison to 10% in non HIV group and this risk remains elevated throughout the course of HIV disease.<sup>5</sup> Prompt diagnosis and treatment are essential to improve drug-resistant TB outcomes, but TB diagnosis in patients with HIV co-infection is challenging, particularly in resource-limited settings. HIV-infected TB patients have higher rates of extra-pulmonary disease, atypical clinical presentations, and normal chest radiographs.<sup>6</sup>

Tuberculosis and HIV control programmes clearly have mutual concerns: the prevention of HIV infection and the treatment of HIV/AIDS should be components of tuberculosis control, and tuberculosis care and prevention should be priorities in the management of HIV/AIDS.<sup>7</sup> TB is the most frequent life-threatening opportunistic disease among people living with HIV and remains a leading cause of mortality, even among persons receiving antiretroviral therapy (ART). Clinical trials have shown that isoniazid preventive therapy (IPT) dramatically reduces the incidence of TB among people living with HIV. A 2004 Cochrane Review found that IPT reduced the risk of TB by 33% overall and by 64% when targeted to people living with HIV who had a positive tuberculin skin test. A recent retrospective study also showed that IPT significantly reduced the incidence of TB even among people living with HIV and receiving ART.<sup>8</sup>

CD4 T cells are critical in the control of *M. tuberculosis* infection, as quantitative and qualitative deficiencies of these effector cells in

HIV-infected individuals increase the rates of both primary and reactivation disease. While the lifetime risk of developing active TB is approximately 10% for immune-competent persons following initial infection, for persons with HIV co-infection the annual risk can exceed 10%, and the risk of TB reactivation rises as the CD4 cell count declines.<sup>2</sup> HIV-infected persons are at risk of TB throughout their course of disease, even after they respond to ART.<sup>9</sup>

In Nepal, the first case was demonstrated in 1988 and the concept of treating HIV infection with highly active antiretroviral treatment (HAART) was introduced quite later.<sup>10</sup> Among those with HIV infection, the CD4+ T-lymphocyte count is the major indicator of immunodeficiency, a main factor in deciding whether to initiate HAART, and an important parameter in monitoring treatment response. Despite current recommendations to start HAART at CD4+ counts of 350 cells/mm<sup>3</sup> or greater, the reality is that many patients, even in developed countries, are still being diagnosed and initiate treatment late in the course of their HIV infection.<sup>11</sup>

Treatment of tuberculosis patients in resource-limited countries with concurrent epidemics of Hepatitis C Virus (HCV), Hepatitis B Virus (HBV), and HIV may be associated with significant hepatotoxicity. Serologic screening of tuberculosis patients for HBV, HCV and HIV or using behavioral algorithms to identify patients in need of intensive monitoring during anti-tuberculosis therapy may reduce this risk.<sup>12</sup>

The present study is focused to find out prevalence of TB among HIV infected individuals, clinical features and ART response on CD<sub>4</sub> cell count.

## METHODOLOGY

**Setting:** The study was carried out in three different places viz. BPKIHS, Dharan; SPARSA Nepal, Kathmandu and Sukhra Raj Tropical and Infectious Disease Hospital, Teku, Kathmandu (TEKU Hospital) from April 2010 to March 2011. It was done with due privacy in their respective VCT Clinic by face to face interview with the HIV infected individuals based on pretested semi-structured questionnaire. Also, an address was given to the past medical documents, for better

authenticity of the information, which most of them had themselves.

**Study subjects:** The target population of the study was the HIV infected persons visiting the VCT Clinic either for taking medications or for follow-up of regular check up during 1 year period. Among those who gave supportive consent, an approach was made to include all individuals whether they were already taking medications or about to start. A total of 313 HIV infected individuals were interviewed.

**Study design and sample size:** This is a cross sectional, descriptive study which includes primary and secondary data. Based on the prevalence of TB co-infection among HIV individuals (33.3%)<sup>1</sup>, the required sample size was calculated as 315 based on the precision of 5.33 (16% of prevalence) at 95% confidence limit after adding 5% for non-response. Two individuals disagreed to participate in the study.

**Exclusion criteria:** Those who didn't give consent and who couldn't report CD<sub>4</sub> count were excluded. The CD<sub>4</sub> count was done by the patients themselves.

**Statistical analysis:** The data was entered into Microsoft Excel 2007 and analyzed in SPSS 17.0. Mean, median and standard deviation were calculated. Mann-Whitney Test and Chi square test were applied to find out statistical significance in numeric and categorical data respectively. Probability of significance was set at 5% level of significance. Odds Ratio (OR) and its 95% confidence interval (CI) were also calculated to examine strength of association between the categorical variables and its' limit.

**Ethical consideration:** Ethical consent was taken from institutional review board BPKIHS, Dharan; SPARSA NEPAL, Kathmandu and Sukhra Raj Tropical and Infectious Disease Hospital (Teku, Kathmandu). Verbal consent was also taken with the individuals who were diagnosed to be HIV infected prior to interview. Privacy of participants was maintained during interview with due consideration of the emotional aspect.

The normal oral or ear temperature is 37° C but may range between 35.8°C and 37.2°C.<sup>13</sup> The temperature more than this was considered to be

fever. Diarrhea was defined as 2 or more loose or watery stools per day for more than 2 consecutive days.<sup>14</sup> Chronic diarrhea was defined as diarrhea persisting for more than 14 days.<sup>15</sup> Tuberculosis co-infection was ascertained by past medical records and history of taking anti-tubercular therapy. HBV and HCV infection were considered positive with respect to serological tests as per medical records. Individuals who gave history of use of syringes for self administration of drugs were considered intravenous drug users (IDU). Most of IDU, but not all, had multiple scar marks on their forearm. The threshold for starting ART was considered to be CD<sub>4</sub> count to be less than 250/μL. Weight loss may be due to lack of food intake (anorexia, dysphasia or vomiting), mal-absorption of nutrients, or a systemic effect of important diseases such as cancer (within or outside the gastrointestinal tract), inflammatory bowel disease or chronic infections such as TB (within or outside the gastrointestinal tract).<sup>16</sup> Weight loss in HIV infected patients can be due to HIV wasting syndrome or due to chronic infections like tuberculosis. HIV wasting syndrome has been defined by the Centre for Disease Control (CDC), USA, as involuntary weight loss greater than 10% of baseline weight associated with either chronic diarrhea for at least 30 days or chronic weakness or documented fever for at least 30 days in the absence of a concurrent illness or condition other than HIV infection that could explain findings (e.g., tuberculosis, cryptosporidiosis, or other specific enteritis).<sup>17</sup> We were mainly focused on weight loss due to tuberculosis.

## RESULTS

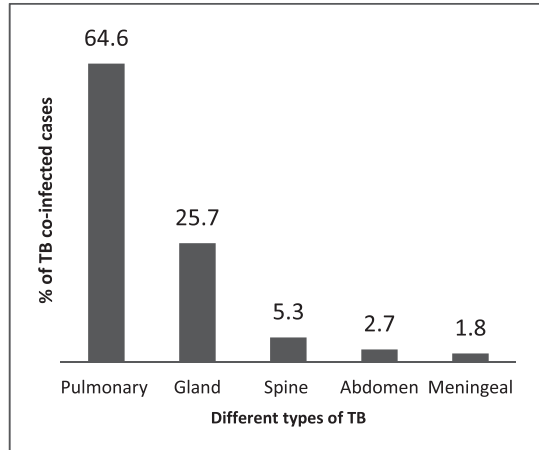
The mean age of the individuals was 33.7 years which ranged from 2 years to 67 years. Around one-third were males. Almost 40% of males and 25.3% of females had TB co-infection. In the study sample, 72.8% were married, 8% were unmarried, 14.1% were single, 5.1% was widow/widower. Of the total sample 65.5% were IDU and 34.5% were non-IDU. Majority of them (94.2%) were receiving ART and 5.8% were to start ART or not taking ART. The study revealed that 36.1% persons were co-infected with tuberculosis. About 5.75% had HBV and 41.53% had HCV infection (Table 1).

There was significant association of TB co-infection among male compared to females

**Table 1.** Socio-demographic profile of HIV infected individuals in three VCT centers who volunteered for the study. (n=313)

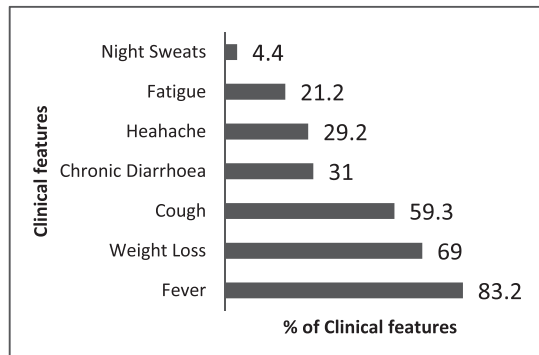
Variables		Frequency	%
Sex	Male	234	74.8
	Female	79	25.2
Marital Status	Married	228	72.8
	Unmarried	25	08.0
	Single	44	14.1
	Widow	6	01.9
	Widower	10	03.2
Living with (for consideration of social support)	Family	193	61.7
	Rehabilitation center	67	21.4
	Alone	51	16.3
	Friends	2	00.6
Reason for First Recognition of Having acquired HIV Infection	Increased Severity of Presenting Illness	180	57.5
	Accidental Examination of Blood	65	20.8
	Spouse Being HIV positive	49	15.6
	Deliberate Checkup for HIV	12	03.8
	Presence of Risk Behavior(s)	7	02.2
TB Co-infection	Yes	113	36.1
	No	200	63.9
IDU	Yes	205	65.5
	No	108	34.5
ART	Being Taken	295	94.2
	Not Being Taken	18	05.8
Hepatitis Co-infection	HBV	18	5.75
	HCV	130	41.503.0
VCT Centers Visited	BPKIHS	65	20.8
	SPARSA Nepal	95	30.4
	TEKU HOSPITAL	153	48.9

(OR=1.95, CI=1.06-2.37, P=0.021). Regarding the clinical feature of HIV individuals, 53.8% had fever, 46.5% experienced weight loss, 41% suffered from chronic diarrhea, 37.2% had cough, 34.4% had rashes, 28.5% had headache, 23.6% used to get fatigue easily, 12.8% had oral lesions, 7.6% had blurred vision, 3.8% genital lesions and 2.8% had night sweats (Table 2). Around two third had pulmonary TB, 25.7% had gland TB, 5.3% had spinal TB, 2.7% had abdominal TB and 1.8% had tuberculosis of Meninges (Figure 1).



**Figure 1.** Different types of TB co-infection (%) among HIV positive individuals in three VCT centers. (n=113).

But among TB co-infected ones the presenting clinical features were quite different. Around 83% had fever, 69% experienced weight loss, 59.3% had cough, 31% suffered from chronic diarrhea, 29.2% had headache, 21.2% used to get fatigue easily, and 4.4% had night sweats (Figure 2.)



**Figure 2.** Clinical presentation HIV infected individuals co-infected with TB in three VCT centers. (n=113).

Fever was found to be significantly associated with TB co-infection (OR=11.27, CI=6.11-20.99, P<0.001). Weight loss was also found to be significantly associated with TB co-infection (OR=5.73, CI=3.36-9.81, P<0.001). Similarly, cough had significant relation with TB co-infection (OR=5.83, CI=3.39-10.05, P<0.001) (Table 2).

Table 3 shows the average CD4 count among those individuals who had TB co-infection was found to be significantly less compared to the individuals who didn't have TB co-infection in case of just before starting ART (P=0.022). Similarly, after six months, the mean CD<sub>4</sub> count was significantly

associated among them ( $P=0.001$ ). But after one year of starting ART, there was no significant association on average CD4 count among the two groups. However, data shows a slight increment in average CD4 count among TB co-infected persons than not infected persons. Similar association was observed after 1.5 years, 2 years, 2.5 years, 3 years and 3.5 years.

Table 4 demonstrates those population who were taking ART, had mean CD4 count of 180.16 (SD=98.97 and median CD4 count= 168) just

before starting ART compared to mean CD4 count of 447.78 (SD=166.05 and median =425) in the individuals who were not taking ART. Mean CD4 count was in increasing pattern without any decline for two and half years among the population taking ART. But in succeeding six months' duration, the mean CD4 count decreased to 379.39 (SD=147.69 and median =376.5). In subsequent six month the mean CD4 count increased to 410.28 (SD=168.47 and median CD4 count=376.5). The mass not taking ART had falling pattern of mean CD4 count for one and half year.

**Table 2.** Clinical features in HIV infected people along with tuberculosis co-infection. (n=113)

Variables Yes(n=113) %		Presence of TB Co-infection		Total (n=313)	OR (CI)	$\chi^2$ value	P value
		No(n=200) %					
Clinical features	Fever	83.2	34.9	155	11.27 (6.11-20.99)	80.18	<0.001
	Weight loss	69.0	32.0	134	5.73 (3.36-9.81)	49.64	<0.001
	Cough	59.3	22.9	107	5.83 (3.39-10.05)	49.55	<0.001
	Chronic diarrhea	31.0	47.4	118	0.63 (0.38-1.06)	3.41	NS
	Headache	29.2	28.0	82	1.27 (0.73-2.20)	0.83	NS
	Fatigue	21.2	25.1	68	0.96 (0.52-1.74)	0.02	NS
	Night sweats	4.4	1.7	8	3.04 (0.62-16.39)	1.44	NS
Sex	Male	39.7	60.3		1.95 (1.06-2.37)	5.329	0.021
	Female	25.3	74.7				

NS-not significant

**Table 3.** Change and comparison of CD<sub>4</sub> cell count in HIV infected persons six monthly, among those who had TB co-infection and those who hadn't, during the course of ART for three and half years. (n=313)

CD4 Count (Six Monthly)	Presence of TB Co-infection		Total	P value
	Yes	No		
Just Before Starting ART (Mean $\pm$ SD), Median, No.	(171.65 $\pm$ 101.48), 161.00, 113	(209.05 $\pm$ 128.95), 182.00, 200	(195.55 $\pm$ 120.94), 172.00, 313	0.022*
At 6 Months' Duration (Mean $\pm$ SD), Median, No.	(251.42 $\pm$ 141.59), 221.00, 106	(281.94 $\pm$ 106.63), 268.00, 184	(270.79 $\pm$ 121.27), 255.50, 290	0.001*
At 1 Year's Duration (Mean $\pm$ SD), Median, No.	** (311.87 $\pm$ 180.88), 283.00, 87	(297.61 $\pm$ 116.67), 304.00, 142	(303.03 $\pm$ 144.24), 293.00, 229	0.576
At 1.5 Years' Duration (Mean $\pm$ SD), Median, No.	(344.92 $\pm$ 172.20), 305.00, 62	(319.52 $\pm$ 129.73), 327.00, 112	(328.57 $\pm$ 146.30), 317.50, 174	0.757
At 2 Years' Duration (Mean $\pm$ SD), Median, No.	(368.42 $\pm$ 187.55), 335.00, 45	(315.82 $\pm$ 123.84), 327.00, 76	(342.07 $\pm$ 153.81), 330.00, 121	0.084
At 2.5 Years' Duration (Mean $\pm$ SD), Median, No.	(433.94 $\pm$ 259.33), 385.00, 18	(372.11 $\pm$ 158.91), 347.00, 38	(391.98 $\pm$ 196.53), 347.00, 56	0.611
At 3 Years' Duration (Mean $\pm$ SD), Median, No.	(448.00 $\pm$ 226.75), 425.00, 8	(359.79 $\pm$ 114.68), 376.00, 28	(379.39 $\pm$ 147.69), 376.50, 36	0.446
At 3.5 Years' Duration (Mean $\pm$ SD), Median, No.	(474.29 $\pm$ 255.59), 617.00, 7	(385.39 $\pm$ 121.13), 384.00, 18	(410.28 $\pm$ 168.47), 387.00, 25	0.363

P value was calculated by Mann-Whitney Test (non-parametric test)

\* Significant value

\*\*After one year of having taken ART, the mean CD4 count became more in TB co-infected individuals compared to those who had no TB co-infection. Then subsequently the mean CD4 count was always at higher level among those who had TB compared to those who hadn't.

**Table 4.** Change and comparison of CD<sub>4</sub> count in HIV infected individuals six monthly, among those who were under ART and those who weren't, during the course of ART for a period of three and half years. (n=313)

CD <sub>4</sub> Count (Six Monthly)	Receiving ART		Total	P value
	Yes	No		
Just Before Starting ART (Mean ± SD), Median, No.	(180.16 ± 98.97), 168.00, 295	(447.78 ± 166.05), 425.00, 18	(195.55 ± 120.94), 172.00, 313	<0.001*
At 6 Months' Duration (Mean ± SD), Median, No.	(268.85 ± 120.68), 255.00, 286	(409.00 ± 86.08), 431.50, 4	(270.79 ± 121.27), 255.50, 290	0.013*
At 1 Year's Duration (Mean ± SD), Median, No.	(300.77 ± 143.20), 291.50, 226	(473.33 ± 144.68), 400.00, 3	(303.03 ± 144.24), 293.00, 229	0.026*
At 1.5 Years' Duration (Mean ± SD), Median, No.	(328.21 ± 146.65), 315.00, 173	-	-	-
At 2 Years' Duration (Mean ± SD), Median, No.	(342.07 ± 153.81), 330.00, 121	-	-	-
At 2.5 Years' Duration (Mean ± SD), Median, No.	(391.98 ± 196.53), 347.00, 56	-	-	-
At 3 Years' Duration (Mean ± SD), Median, No.	** (379.39 ± 147.69), 376.50, 36	-	-	-
At 3.5 Years' Duration (Mean ± SD), Median, No.	(410.28 ± 168.47), 387.00, 25	-	-	-

P value was calculated by Mann-Whitney Test (Non-parametric test)  
 \* Significant value  
 \*\*Sudden decline in mean CD<sub>4</sub> count at the time of three years after gradual increase in preceding two and half years.

## DISCUSSION

The present study estimated the prevalence of TB co-infection among HIV positive individuals to be 36.1 % in context Nepal which is consistent with worldwide statistics.<sup>1</sup> There was significant association of TB co-infection among male compared to females (OR=1.95, CI=1.06-2.37, P=0.021). Among TB co-infected cases, fever was the commonest clinical feature, followed by weight loss and cough. A night sweat, which was considered as one of the constitutional symptoms didn't have dominant figure in this study.

Other symptoms among the cases were chronic diarrhea (31 %), headache (29.2%), easy fatigue (21.2%) and night sweats (4.4%). However only fever, weight loss and cough were the significant symptom associated with TB co-infection. The clinical presentation of TB in HIV infection is affected by the degree of underlying immune suppression.<sup>5</sup> Our study is consistent with this fact because we found that the mean CD<sub>4</sub> counts of the patients co-infected with TB being much less than in those who were not. Of all symptoms, weight loss can be of utmost important. Studies have repeatedly documented that the existence and magnitude of weight loss predict morbidity and

mortality.<sup>18,19</sup> Correlations have been established between high HIV viral load, low CD4 cell counts, and weight loss. In HAART experienced patients with suppressed plasma viral load, weight loss has been attributed to the persistence of HIV in peripheral blood monocytes and macrophages. The persistence of HIV leads to excessive cytokine activation and dysregulation, and this in turn triggers various metabolic abnormalities that lead to weight loss such as increase in resting energy expenditure, proteolysis, and hypercatabolism.<sup>17</sup> A study reported that as little as 5% of weight loss over 4 months was associated with decreased survival.<sup>20</sup>

We also found that the majority of the patients lived with family .i.e. the major bulk of HIV infected patients had good support from the family as 61.7% lived with their family. Had there been no co-operation from the family, they would not be staying along with the family members. Stay in rehabilitation center counted for second largest population (21.4%). It was due to the reason that they wanted to live with individuals having same disease so that they could share their feelings and learn more about the disease. Also, a good number of populations lived alone (16.3%) which may be indicative of lack of social support. Environmental

social determinants, such as housing conditions, social networks, and social support, are also key drivers for HIV/AIDS, viral hepatitis, STDs, and TB. Kidder et al. conducted a study among housed and homeless individuals with HIV/AIDS and found that homeless people with HIV/AIDS had poorer health status, were less adherent to medication regimens, and were more likely to be uninsured and to have been hospitalized.<sup>21</sup>

There is effect of tuberculosis on mortality in HIV positive people. A Meta-Analysis shows that people living with HIV (PLWH) with TB face an approximately two times higher risk of death from all causes compared to PLWH without TB. The increased hazard of mortality implies that PLWH with TB die earlier compared to PLWH without TB.<sup>22</sup> In our study more than one third (36.1%) persons were co-infected with TB.

Our study revealed that nearly two third (64.6%) of TB infected patients had pulmonary TB followed by gland TB (25.7%) and spinal TB (5.3%). This supports that prime concern of co-infection of TB in HIV positive individuals is that of pulmonary TB followed by gland TB. At CD4+ cell counts greater than 350/ $\mu$ L, TB disease is most often limited to the lungs, histopathologic results are similar to those in HIV-seronegative patients (i.e., granuloma with or without caseation), and extra-pulmonary involvement, when present, usually is nodal or pleural (Burman and Jones, *Semin Respir Infect*, 2003). In advanced HIV infection, pulmonary involvement is still the most common TB presentation; however, extra-pulmonary involvement is observed in approximately 70% of patients with CD4+ cell counts less than 100/ $\mu$ L, and up to 50% of those with CD4+ cell counts greater than 50/ $\mu$ L will have positive TB blood cultures.<sup>5</sup>

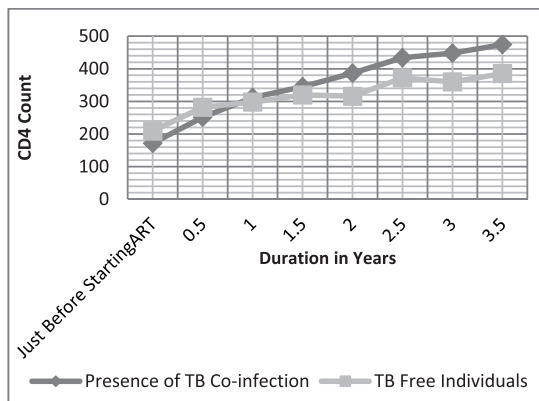
With proper treatment, a person with infectious tuberculosis very quickly becomes non-infectious – probably most often in less than two weeks – and so can no longer transmit infection to others.<sup>7</sup> Highly active antiretroviral therapy (HAART) improves the immune function and decreases morbidity, mortality and opportunistic infections in HIV-infected patients. HAART improves immune function by suppressing HIV viral replication and increasing CD4+ T-cell counts.<sup>23</sup>

With respect to our study- before starting ART, the average CD4 count was found to be significantly less among TB-HIV co-infected patients compared to those who didn't have TB co-infection. Similarly, after six months, the mean CD4 count was significantly associated among the two groups. After one year of having taken ART, the mean CD4 count became more in TB co-infected individuals compared to those who had no TB co-infection. Then subsequently the mean CD4 count was always at higher level among those who had TB compared to those who hadn't.

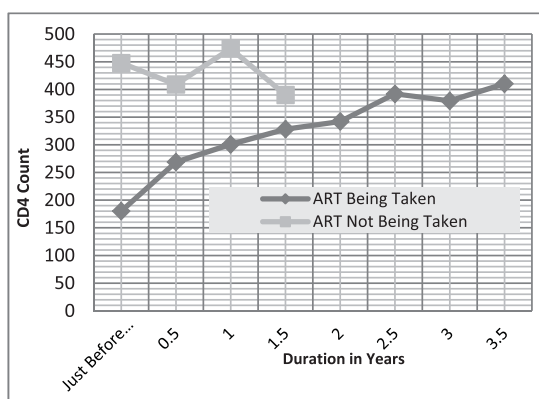
The risk of TB following *M. tuberculosis* infection is determined mainly by the individual's immune status (and hence HIV infection is a potent risk factor for tuberculosis).<sup>6</sup> It was found that the mean CD<sub>4</sub> count was in increasing pattern without any turn down for three and half years among TB co-infected individuals, but the group which were TB free had fluctuating mean CD4 count. This shows that there is marked increase in CD4 count in TB co-infected individuals despite lower initial CD4 count before starting ART. But after three and half years the variation is somewhat similar. Studies of the kinetics of CD4+ count response post-HAART indicate that the CD4+ count increases rapidly during the first 3-6 months, in part due to release of memory T-cells from lymphoid tissue, and then increases slowly during the next 3-4 years, reflecting reconstitution of the immune system. The magnitude of CD4+ recovery may depend on a variety of factors, including maintenance of virologic suppression, age, and CD4+ count at HAART initiation.<sup>11</sup>

There are no validated markers to differentiate those who will have a more robust CD4 response to ARV from those who will not.<sup>24</sup> Antiretroviral drug concentrations are among the most important determinants of clinical response to a drug accounting for both toxicity and efficacy.<sup>25</sup> We also tried to see pattern of change of mean CD<sub>4</sub> count among different type of TB co-infection. Those people who had pulmonary TB, had mean CD4 count of 157.86 just before starting ART compared to mean CD4 count of 214.21 in the individuals who had TB of gland and 127.17 in the individuals who had TB of spine. The mean CD<sub>4</sub> count of 157.86 for pulmonary TB is quite low as compared to other similar studies. It could have been so because there

was also hepatitis infection among the volunteers of the study. Among TB co-infected individuals, 6.2% had HBV alone, 38.9% had HCV alone and 2.7% had both HBV and HCV infection. Another explanation could be that TB facilitates HIV viral replication to a greater extent in the earlier stages of HIV infection than during advanced illness, when viral replication is already at its peak.<sup>26</sup> We found that the mean CD4 count was in rising pattern without any decline for three and half years among the population with pulmonary TB, but the ones having TB of gland also had rising pattern of mean CD4 count but only for two years. Then the mean CD4 count had falling pattern till three and half years. The mass of people having TB of spine had fluctuating pattern of mean CD4 count as shown in figure 3.



**Figure 3.** Change and comparison of mean CD<sub>4</sub> cell count in HIV infected individuals six monthly, among those who had TB co-infection and those who hadn't, during the course of ART for a period of three and half years. (n=313).



**Figure 4.** Change and comparison of mean CD<sub>4</sub> cell count in HIV infected individuals six monthly, among those who were taking ART and those who weren't taking ART, during the course of ART for a period of three and half years. (n=313).

The question of whether those initiating HAART will continue to increase their CD4+ count after 4-5 years or will plateau has been debated in the literature, and remains unclear. Some studies have suggested that normalization of CD4+ counts in HIV-infected persons can be achieved if viral suppression with HAART can be maintained for a sufficiently long period of time.<sup>11</sup> Several factors such as age, ethnicity, body weight and patients' immune status may influence antiretroviral drug concentrations.<sup>25</sup> In our study, those who were taking ART had mean CD4 count of 180.16 just before starting ART compared to mean CD4 count of 447.78 in the individuals who were not taking ART. We found that the mean CD4 count was in increasing pattern without any decline for two and half years among the population taking ART whereby the mean CD4 count was 391.98. But in succeeding six months' duration, the mean CD4 count decreased to 379.39. In subsequent six month the mean CD4 count increased to 410.28. The mass not taking ART had falling pattern of mean CD4 count for one and half year (Table 3). In one study, after > 5 years on HAART, patients with viral suppression who started at <200 cells/mm<sup>3</sup> had an adjusted annual increase of 32 cells/mm<sup>3</sup>, attaining an average CD4+ count of 497 cells/mm<sup>3</sup>. Another study statistically estimating the CD4+ trajectory concluded that those starting HAART at <200 CD4+ cells who remained on therapy would continue to increase through 7 years, although 25% still had <350 cells at 7 years. One small study of 16 patients followed for up to 10 years with strict viral control based on HIV RNA detection using ultrasensitive techniques showed continued positive increases in CD4 + counts, although this study represented a small group of highly selected patients.<sup>11</sup>

On the other hand, other studies report that the average CD4+ count may level off after 4-6 years following HAART initiation, even among patients with viral suppression. Given this leveling off, many patients who start at lower CD4+ counts, even after years on HAART with early CD4+ increases, may fail to reach a normal CD<sub>4</sub>+ threshold. In one study of those with sustained viral suppression who started HAART at <200 CD4+ cells/mm<sup>3</sup>, after 6 years only 42% had > 500 CD4+ cells/mm<sup>3</sup>, and only 12% had >750 cells/mm<sup>3</sup>. In another study, 44% of those starting therapy with a CD4+ count <100 cells/mm<sup>3</sup> and 25% of those starting HAART



with a CD4+ count of 100–200 cells were unable to achieve a CD4+ cell count >500 cells/mm<sup>3</sup> over a mean follow-up of seven years, and many did not reach this threshold by year 10.<sup>11</sup>

Antiretroviral therapy improves survival in HIV-positive patients. In addition, antiretroviral therapy reduces TB rates by up to 90% at an individual level, by 60% at a population level and it reduces TB recurrence rates by 50%. ART should be initiated for all people living with HIV with active TB disease irrespective of CD4 cell count. TB treatment should be started first, followed by ART as soon as possible and within the first 8 weeks of starting TB treatment.<sup>27</sup>

Despite several explanations, the most important aspect is the survival the HIV infected individuals. Death rates in HIV-positive individuals remain elevated compared to those in the general population and it is believed that HIV may play a role in the development of several serious non-AIDS conditions. Thus, combination ART may have a greater positive impact on the health of HIV-positive individuals than anticipated, which may now justify its earlier use.<sup>28</sup>

The dramatic scale-up of ART in resource-limited settings has brought not only TB treatment but also prevention of TB in HIV-infected persons to the forefront. TB prevention strategies with known efficacy include rapid identification and treatment of active TB cases (in source patients), infection-control measures to reduce nosocomial transmission of TB and ART to reduce the incidence of TB among HIV-infected patients. Research priorities in TB prevention center on adapting and improving these known strategies for HIV infection in resource-limited settings.<sup>9</sup>

## CONCLUSION

TB and HIV co-infection is an emerging medical issue in Nepal. The prevalence of TB co-infection among HIV cases is found to be 36.1%. Consideration of TB need to be made while caring patients with HIV infection and vice versa. Timely given ART can be of utmost significance so it should be initiated when CD4 cell count falls below the cut off value. Preventive, promotive and curative aspects of TB and HIV should be undertaken hand in hand so that both of these entities are addressed simultaneously.

## ACKNOWLEDGEMENTS

Had there been no support from SPARSA Nepal (Kathmandu), Sukraraj Tropical and Infectious Disease Hospital (Teku, Kathmandu) and BPKIHS, Dharan; the study could not have been completed. A sincere gratitude to all the HIV infected individuals who kindly co-operated for the study despite ill health. Due concern is expressed to all the crew members of the study group. Special thanks to Prof. Suman Rijal and Dr. Naveen Pandey from Department of Internal Medicine, BPKIHS for kind co-operation.

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Case Report

## A RARE EXTRA-PULMONARY PRESENTATION OF TUBERCULOSIS AS GUM TUBERCULOSIS

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### ABSTRACT

Tuberculosis (TB) is a chronic granulomatous disorder presenting mostly (80%) as a pulmonary disease, the extra-pulmonary presentation being relatively uncommon. The oral cavity can sometimes be a site for extra-pulmonary tuberculosis with a highly variable clinical presentation including ulceration, diffuse inflammatory lesions, granulomas and fissures. Oral lesions usually appear secondary to a primary tubercular infection elsewhere, although primary infection of the oral mucosa by *Mycobacterium tuberculosis* has been described. We report here a rare case of primary tuberculosis of the hard palate extending to gingiva, manifesting as gingival enlargement with ulceration. Diagnosis was established by histopathological examination of tissue biopsy and by chest radiography. The patient was put on anti-tubercular therapy for nine months to which a prompt response was obtained. This emphasizes the need to consider tuberculosis in the differential diagnosis of non-healing mucosal lesions of oral cavity for early diagnosis and prompt treatment.

**Key words:** Gingiva, Oral Cavity, Tuberculosis

### INTRODUCTION

Tuberculosis is a major public health concern especially in India, and is still among the most life-threatening infectious diseases, resulting in high mortality in adults. With a prevalence of 200 cases per 100 000 population in 2009 globally, it is estimated that two billion people (i.e. one-third of the world's population) have been in contact with the tubercle bacillus. The two countries with the largest number of incident cases in 2009 were India and China, India alone accounting for an estimated one fifth (21%) of all TB cases worldwide. Moreover, the emergence of drug-resistant TB has recently raised serious concerns. There were an estimated 440 000 cases of multi-drug resistant TB (MDR-TB) in 2008, approximately 25% of them

being in India.<sup>1</sup> Oral TB accounts for 0.1–5% of all TB infections according to varied reports.<sup>2</sup> Although oral manifestations of TB have been rare in recent years, they are re-appearing on account of the emergence of the global pandemic of HIV and the rampant drug resistance in tubercle bacilli.<sup>3</sup> Oral TB accounts for up to 1.33 % of HIV-associated opportunistic infections.<sup>4</sup> Hence, it is important to consider tuberculosis as a differential diagnosis of oral lesions especially in regions of high incidence of tuberculosis like India. We are presenting here a rare case of primary oral tuberculosis of the hard palate that underlines the importance of the above statement.

### Case presentation

A 26 year old female patient had developed a diffuse, painless, erythematous swelling of the mucosa of hard palate extending anteriorly behind the incisors over a period of 2 years and progressing to ulceration for which she consulted a dentist. She also had systemic complaints of low grade fever, weight loss, loss of appetite. The dentist found no evidence of cervical lymphadenopathy and noted that there was no history of any dental procedures

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or trauma. The patient was treated empirically with antibacterial agents for 1 week with no response. A radiograph of the upper mandible found no bony erosions. She was later put on antifungal therapy and the exudate was sent for potassium hydroxide staining to identify fungal infection but report came back negative. By this time her disease had progressed to involve gingiva and periodontal tissue and 4 upper incisors were unsalvageable and had to be removed. She was then referred to us to rule out tuberculosis. When she presented to us she had an erythematous swelling over hard palate extending to alveolus anteriorly. Rest of the oral cavity was clean. She had no past history of tuberculosis and was adequately vaccinated with BCG. A chest radiograph was obtained and found to be clear with nothing to suggest a primary focus of tuberculosis in the lungs. The patient was found to be non-reactive for HIV serology. We started by taking a biopsy of the lesion, which on histopathological examination showed non caseating epitheloid cell granulomas suggestive of tuberculosis. Infection with mycobacterium tuberculosis was further confirmed by PCR studies of the specimen as well. There was no evidence of malignancy (Figure 1).

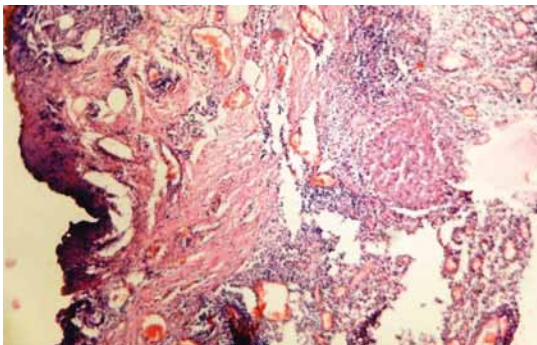


Figure 1(a) Haematoxylin and Eosin stained histopathological section of lesion biopsy at 10X

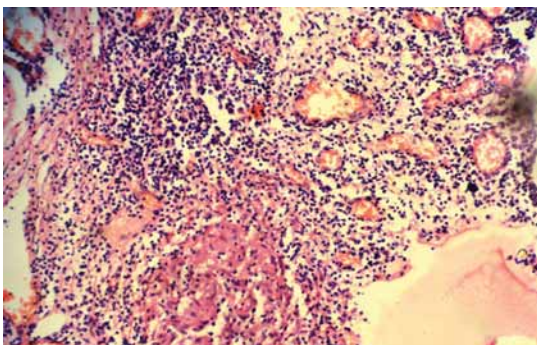


Figure 1(b) Magnifications respectively, showing non caseating epitheloid cell granulomas under light microscopy at 40X

She was subsequently put on anti-tubercular therapy (ATT) with isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE) for 3 months. By the end of 2 months of starting ATT the lesion had reduced in size and the patient was improving symptomatically. She later received a continuation therapy with isoniazid and rifampicin for 6 months. On subsequent follow up the lesion completely resolved and the patient is currently under follow up.

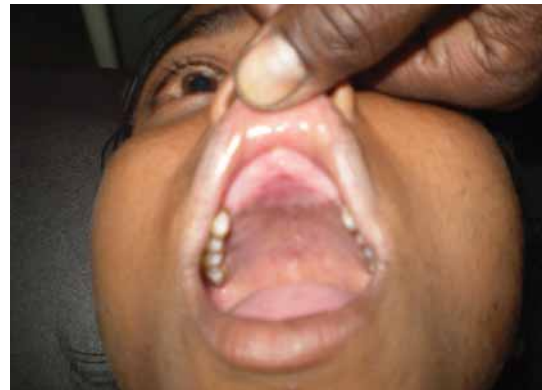


Figure 2 (a) before treatment



Figure 2 (b) after treatment

## DISCUSSION

Although oral tuberculosis has been well documented with an incidence of accounting to 0.1-5% of all tuberculosis cases,<sup>2</sup> tuberculous lesions of the upper aerodigestive tract have become rare.<sup>5</sup> Tuberculous lesions of the oral cavity may be either primary, or secondary to disease elsewhere in the body, with secondary lesions being more common.<sup>6</sup> Oral tuberculosis most commonly presents as ulcerations, typically as a stellate ulcer on the dorsum of the tongue with undermined edges, sloughed or granulated floor and indurated base. However, it can also present as swelling, nodules, discharge, fistulas or even

diffuse inflammation of the oral cavity.<sup>2</sup> Although the tongue is the commonest site for oral tuberculous lesions, they may also affect the mandible, gingiva, buccal mucosa, floor of mouth, lips and palate.<sup>2,7-11</sup> The hard palate is the rarest of all sites of oral involvement and was cited as the main or initial site of presentation of the oral TB lesion in 5% of the case reports<sup>12</sup> according to a recent systematic review with 50% of the cases having evidence of a primary pulmonary pathology.<sup>2</sup> Thus the present case report is one of the rarest presentations of tuberculosis.

The differential diagnosis of a tuberculous ulcer of the oral cavity includes aphthous ulcers, traumatic ulcers, syphilitic ulcers and malignancy.<sup>5</sup> It is most likely that tuberculosis is only considered when the histological specimen reveals a granulomatous lesion. The diagnosis of tuberculosis is confirmed by the presence of acid-fast bacilli in the specimen, or more likely by culture of tubercle bacilli. Since oral tuberculosis is almost always secondary to pulmonary tuberculosis, sputum culture must also be carried out. Radiographic evidence of tuberculosis must also be sought. According to a recent review of the reported cases of oral tuberculosis symptoms had been present for an average of 6 months before diagnosis, 30% of these received antibiotic and/or antifungal therapy, 15% received corticosteroids or analgesic/anti-inflammatory drugs while most of these cases were labelled as non-healing or unresponsive to treatment.<sup>2</sup> The picture is very similar to the case presented here, which was previously misdiagnosed and treated inappropriately with antibiotics before we established the diagnosis of tuberculosis. This clearly emphasizes the importance of considering tuberculosis as a differential diagnosis in chronic oral lesions as well as calls for better co-ordination between dentists and physicians so as to ensure early diagnosis and prompt treatment of this disorder especially since it is an extremely treatable condition with cure rates approaching 85%.<sup>2</sup>

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Case Report

## LARYNGEAL TUBERCULOSIS PRESENTING WITH PRIMARY SYMPTOMS OF LARYNGEAL CARCINOMA

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### ABSTRACT

Laryngeal tuberculosis (TB) occurs in about 1% of patients suffering from pulmonary tuberculosis; however presentation of these patients with primary laryngeal symptoms is a rarity. In such situations it forms a diagnostic dilemma between laryngeal TB and the more common laryngeal carcinoma.

Highlighting this dilemma we present our patient, a 76 year old male, farmer presenting with primary complaints of progressive dysphagia for 3 weeks. This patient happens to be our second case of laryngeal TB, presenting with primary laryngeal symptoms in a span of under 2 years.

We present these cases to emphasize that although laryngeal tuberculosis presenting with primary laryngeal symptoms is a rarity, it must be considered when evaluating dysphagia or dysphonia in populations where TB is endemic.

### INTRODUCTION

Laryngeal tuberculosis (TB) considered to be rare sequelae of pulmonary TB; occurs in about 1% of patients suffering from pulmonary infections.<sup>1,2</sup> However presentation of patients with primary laryngeal symptoms such as dysphagia or dysphonia is a rarity. In such situations it forms a diagnostic dilemma between laryngeal TB and the more common laryngeal carcinoma (LCA). Further compounding this situation<sup>3</sup> is the similar distribution of risk factors and socio-demographic characteristics that both these diseases thrive in.<sup>4</sup>

Highlighting the aforementioned dilemma we present our second case of laryngeal TB, presenting with primary laryngeal symptoms in a span of under 2 years.

### Case

A 76 year old male, farmer from Karachi, was referred to our clinic by a primary care physician due to progressive dysphagia for the past 3 weeks.

The dysphagia began as intolerance to solid and semi-solid food; which had progressed to the point where he had not been able to tolerate a liquid diet for the past 2 days. Focused history revealed that he had developed gradually progressive hoarseness over the past 6 months. He initially managed the hoarseness with home remedies, including honey and warm water gargles, but this did not seem to alleviate his symptoms. He also developed dyspnea on severe exertion during this period.

On review of systems the patient denied any history of fever, hemoptysis or stridor; however he complained of intermittent bouts of cough which were relieved with medications from a local Hakeem (traditional healer). His family had also noticed a subjective weight loss (he did not have a previously recorded weight for comparison) and fatigability in past few weeks.

The patient did not recall any significant past medical and surgical issues or exposure to tuberculosis (TB). He had an 80 pack year history of smoking, intermixed with the use of water pipes and unfiltered cigarettes.

On examination he appeared drowsy but arousable. Ear, nose and oral cavity examination was within normal limits. Indirect laryngoscopy revealed pooling of saliva. A fiber optic laryngoscopy was performed which revealed supraglottic inflammation with pooling of saliva and diffuse edema over both false cords. The entire length of the true vocal cords could not be visualized; however they were mobile. Granulations were noted along the right vocal cord and post cricoid area. The patient was immediately admitted for rehydration and planned for direct laryngoscopy with biopsy.

Pre-operative evaluation showed hemoglobin of 8.1mg/dl, blood urea nitrogen of 44 mg/dl and creatinine of 1.8 mg/dl. His electrolytes and blood sugar levels were within normal range. Chest X-ray revealed bilateral infiltrates, with multiple cavitary infiltrates suggestive of active tuberculosis. The patient was immediately shifted to an isolation room and a pulmonology consult was generated.

It was decided to proceed with direct laryngoscopy and biopsy with the addition of bronchoscopy and bronchoalveolar lavage (BAL). Direct laryngoscopy revealed granulations along the arytenoids and post cricoid area along with diffuse swelling over the false cords. The aryepiglottic folds, epiglottis and piriform sinus were devoid of disease. A biopsy was taken from the visualized granulations and sent for Ziehl-Neelsen staining, acid fast bacilli culture, fungal staining, fungal culture and histopathological examination. Bronchoalveolar lavage was also sent for cytology and culture.

Postoperatively the patient was shifted back to an isolation room and started on empiric anti tuberculous therapy (ATT). Ziehl-Neelsen staining of the biopsy sample and cytology of BAL fluid was positive for acid fast bacilli. He was discharged on post-operative day 3 after adequate hydration and a provisional diagnosis of tuberculosis. He was started on ATT and advised monthly follow up visits with transmission precautions at home.

Histopathological examination of the excised tissue revealed giant cells with caseous necrosis, no signs of malignancy were noted (Figure 1). Tissue culture revealed heavy growth of acid fast bacilli.

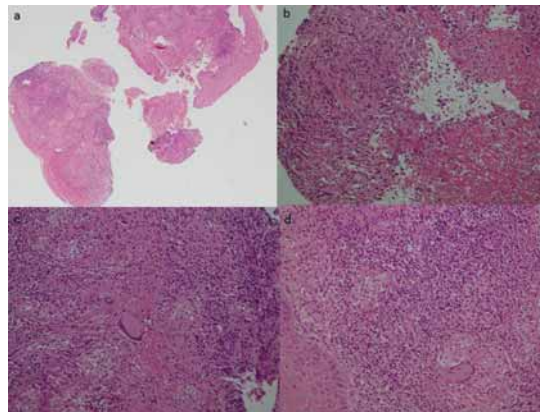


Figure 1. Histopathological examination of laryngeal biopsy specimen, a) hematoxylin and eosin stain at low power showing granulomatous inflammation, b) Foci of necrosis are seen on right lower side, c) horse-shoe shaped giant cell is seen in the center, d)granulomas comprising of giant cells, epithelioid cells and histiocytes can be visualized.

At one month follow up the patient's dysphagia had resolved. Fiber optic laryngoscopy showed minimal granulation, with persistent edema. No pooling of saliva observed.

## DISCUSSION

Having the 8<sup>th</sup> highest estimated prevalence of tuberculosis in the world; Pakistan accounts for 44% of tuberculosis cases in the Eastern Mediterranean Region.<sup>5</sup> Interestingly the same population has one of the highest age- standardized rates of head and neck cancer an estimated 22.5/100,000 in males and 20.4/100,000 in females. The same database reported that laryngeal carcinoma was the 3<sup>rd</sup> most common cancer among males overall in the city of Karachi.<sup>6</sup> Interestingly, both the diseases may have similar presentations, and their risk factors seem to be concentrated in the same population, creating a diagnostic dilemma.

It is hypothesized that laryngeal tuberculosis most commonly occurs due to hematogenous dissemination or direct extension of a primary pulmonary TB infection. Considering this hypothesis to be valid most patients with laryngeal tuberculosis should present with signs and symptoms of their primary pulmonary TB. However patients may present without manifestations of pulmonary TB with complaints of dysphagia and/or dysphonia.

Highlighting the aforementioned dilemma, we present our second case of laryngeal TB, with characteristic presenting features of LCa. Our first patient described earlier was a 40 year old male, presenting with persistent hoarseness and weight loss; without associated fever, night sweats, cough or dysphagia. The previous patient did not have any history of tobacco or irritant use; however considering the absence of associated symptoms and characteristic history he was initially worked up for laryngeal carcinoma.<sup>4</sup>

This patient as well presented with progressive dysphagia, hoarseness and dyspnea on exertion. Although he did not have any fever, hemoptysis or stridor; he complained of intermittent bouts of cough which were relieved with medications from a local Hakeem (traditional healer). In retrospect this could have been used as a pointer towards pulmonary TB. However it seemed unlikely when considering the negative exposure history along with the 80+ pack year history of smoking. This time around we were more likely and convinced while starting empiric ATT prior to the biopsy, based on our previous experience.

In both cases our patients had significant risk factors for both laryngeal TB and LCa. We present these cases to emphasize that although laryngeal

tuberculosis presenting with primary laryngeal symptoms is a rarity, it must be considered when evaluating dysphagia or dysphonia in populations where TB is endemic.

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Review Article

## TUBERCULOSIS PROBLEM IN DAKAHLIA GOVERNORATE, EGYPT

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### ABSTRACT

Tuberculosis (TB) is a potentially fatal contagious disease that can affect almost any part of the body but is mainly an infection of the lungs. It has been present in humans since antiquity. In the past, tuberculosis has been called consumption, because it seemed to consume people from within, with a bloody cough, fever, pallor, and long relentless wasting. In Egypt, TB constitutes the second most important public health problem after schistosomiasis. Although Egypt has relatively low levels of TB according to data from the World Health Organization, 2005:66% of TB cases occur among the socially and economically productive age groups of 15 to 54 years. According to Ministry of Health and Population (MOHP), Egypt; tuberculosis control is carried out through 111 chest centers and 39 chest disease hospitals. Treatment failure accounts for 3%–5% of the treatment outcome of new smear positive cases and 13%–17% of re-treated cases and this is due to non-compliance to treatment, deficient health education to the patient, poor patient knowledge regarding the disease and diabetes mellitus as co-morbid. The incidence and prevalence of tuberculosis in Egypt has been declining due to increased efforts of the MOHP. Prevalence dropped from 88/100,000 population in 1990 to 24 in 2008, according to data from WHO.

**Key words:** Tuberculosis, Problem, Egypt

### INTRODUCTION

Tuberculosis (TB) is a growing international health concern. It is a big killer among the infectious diseases in the world, despite the use of a live attenuated vaccine and several antibiotics. After years of decline, TB has re-emerged as a serious public health problem worldwide, especially with increased drug resistance among *Mycobacterium tuberculosis* (MTB) strains which hinders the success of TB control programs.<sup>1</sup>

#### Interesting facts regarding tuberculosis

Nearly one percent of the world's population is newly infected with TB each year. Every second, someone in the world is newly infected with TB.

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Six to eight million new cases of TB are diagnosed each year. Two hundred million people worldwide, or 10% of those infected, will develop active TB and be able to infect others for 3 decades if not treated. TB spreads through the air and is highly contagious. On average, a person with infectious TB infects 10-15 others every year. TB kills 8,000 people a day - that is 2-3 million people each year. It kills more people than either AIDS or malaria. In fact, TB is the biggest killer of young people and adults in the world today. In the last 100 years, 200 million people have died of TB. People infected with TB do not necessarily become ill- the immune system creates a barrier around the bacilli that can remain dormant for years. 10% of infected people (who do not have HIV/AIDS) develop active TB at some point during their lifetime.<sup>2</sup>

Tuberculosis is a contagious disease, like the common cold; it spreads through the air when droplet nuclei are inhaled. The most effective (infective) droplet nuclei tend to have a diameter of 5 µm and generated during talking, coughing and

sneezing. Coughing generates about 3000 droplet nuclei, while talking for 5 minutes generates 3000 droplet nuclei but singing generates 3000 droplet nuclei in one minute. Sneezing generates the most droplet nuclei by far, which can spread to individuals up to 10 feet away.<sup>3</sup> Each droplet may transmit the disease, since the infectious dose of the disease is very low and inhaling less than ten bacteria may cause an infection<sup>4</sup>. Transmission can only occur from people with active not latent TB.<sup>5</sup>

In the 17<sup>th</sup> and 18<sup>th</sup> centuries, TB caused one fourth of the adult's death in Europe. Between 1953 and 1984, the incidence of the disease steadily decreased about 5-6% every year because of sanitarial improvement, nutrition, ventilation and later because of anti-tuberculous drugs.<sup>6</sup>

Para-aminosalicylic acid (PAS) was discovered in 1940, Isoniazid (INH) in 1952 and Rifampicin in 1960. The introduction of pharmacologic treatment has decreased the incidence of tuberculosis, with predictions of possible eradication. Tuberculosis incidence rates stabilized in most of the world, with increases in African countries and Eastern Europe in recent decades. This tuberculosis reappearance was caused by the AIDS pandemic, emergence of resistant bacilli, human migration patterns, and world poverty.<sup>7</sup>

It is estimated that deaths from TB will increase from 3 million a year currently to 5 million by the year 2050.<sup>8</sup> Between 2002 and 2020, approximately one billion people will be newly infected, 200 million people will get sick and 36 million will die of TB if proper control measures are not instituted.<sup>9</sup>

### Other names of TB

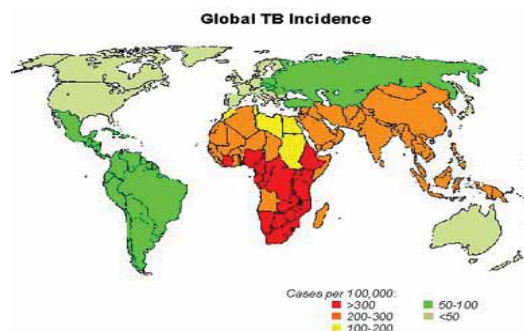
In the past, tuberculosis has been called **consumption**, because it seemed to consume people from within, with a bloody cough, fever, pallor, and long relentless wasting. Other names included **phthisis** (Greek for consumption) and **phthisis pulmonalis**; **scrofula** (in adults), affecting the lymphatic system and resulting in swollen neck glands; **tabes mesenterica**, TB of the abdomen and **lupus vulgaris**, TB of the skin; **wasting disease**; **white plague**, because sufferers appear markedly pale; **king's evil**, because it was believed that a king's touch would heal scrofula; and **Pott's disease**, TB of the spine and joints.<sup>10</sup>

### Geographic distribution

Tuberculosis is prevalent in Russia, India, Southeast Asia, sub-Saharan Africa, and parts of Latin America. The highest number of deaths occurred in the Africa region, where HIV has led to rapid growth of the TB epidemic.<sup>11</sup>

In developing countries, there is an annual incidence of 100 to 450 new cases per 100,000 inhabitants, with 2 to 3 million deaths per year, and 75% of cases affect people between 15 and 50 years of age. Conversely, developed countries have a lower incidence, with 7 to 15 new cases per 100,000 inhabitants and 40,000 deaths per year, the elderly, ethnic minorities and immigrants are chiefly affected.<sup>7</sup>

In 2007, the prevalence of TB per 100,000 people was highest in sub-Saharan Africa, and was also relatively high in Asia. The annual incidence rate varied from 363 per 100,000 in Africa compared to 32 per 100,000 in the Americas. India had the largest total incidence, with an estimated 2.0 million new cases in that year.<sup>12</sup>



**Figure 1.** The following ten countries account for the largest number of TB cases among immigrants: Mexico, Philippines, Vietnam, India, China, Haiti, South Korea, Guatemala, Ethiopia, and Peru.<sup>13</sup>

**Mycobacterium tuberculosis** is the causative agent of most cases of tuberculosis.<sup>15</sup> It is a small bacillus that can withstand weak disinfectants and can survive in a dry state for weeks, protected by a complex and hardly penetrable cell wall. Its special structure is the reason for the resistance to external factors and for the inefficient uptake of antibacterial substances.<sup>14</sup>

The rapid and accurate detection of TB is essential for management of patients and public health control.<sup>15</sup>

In many countries diagnosis of TB is performed by microscopic examination of a stained sputum smear by the Ziehl-Neelsen (ZN) method. Although easy to perform and specific, it lacks sensitivity, requiring  $\geq 10,000$  bacilli per ml of sputum to become positive.<sup>16</sup>

The gold standard for TB diagnosis is the cultivation of *M.tuberculosis*. It is much more sensitive than microscopy and it allows recovery of the bacteria for other studies, such as drug susceptibility testing and genotyping.<sup>17</sup> It can detect 10-100 organisms per/ml however, it is time consuming and takes 6 to 8 weeks for the results.<sup>18</sup>

Lack of sensitivity in smear examination, non-specificity of radiological findings, extended time of *M.tuberculosis* culture and difficulties in diagnosing paucibacillary; childhood and extra pulmonary tuberculosis have necessitated exploring the utility of immunodiagnosis of tuberculosis for definite diagnosis.<sup>19</sup>

Serological methods are simple, rapid, inexpensive, and relatively non-invasive. They can potentially distinguish between active disease and asymptomatic infection<sup>20</sup>. Many tests are available for diagnosis of TB. Most of these tests are based on the detection of IgG, IgA and IgM antibodies to specific mycobacterial antigen or mixture of antigens.<sup>19</sup>

Molecular diagnosis of tuberculosis has enabled rapid detection of *M.tuberculosis* complex in clinical specimens, identification of mycobacterial species, detection of drug resistance, and typing for epidemiological investigation.<sup>21</sup>

Many molecular methods have been developed; these methods can potentially reduce the diagnostic time from weeks to days. PCR-based sequencing has become commonly used to identify many mycobacterial species. DNA probes have been widely used for species determination of the most commonly encountered mycobacteria. High-density oligonucleotide arrays (DNA micro arrays) also have been applied.<sup>22</sup>

### **TB problem in Mansoura**

Tuberculosis is one of the important public health problems<sup>23</sup>. It constitutes a major public health problem after HCV and bilharziasis.<sup>24</sup>

Although Egypt is not on the WHO list of 22 high-TB-burden countries, it is considered one of the high-burden countries in WHO's Eastern Mediterranean region.<sup>23</sup>

Tubercular decay has been found in the spines of Egyptian mummies from 3000–2400 BC.<sup>25</sup> The first evidence that human tuberculosis was present in ancient Egypt came from typical macroscopic osseous changes in human remains, which were in this instance the well preserved Egyptian mummies.<sup>26</sup>

Within the last few years a considerable number of molecular studies have provided evidence for the presence of *M. tuberculosis* complex DNA in ancient skeletal and mummified material.<sup>25</sup>

Tuberculosis is one of the important public health problems in Egypt. However, limited information on the *M.tuberculosis* genotypes circulating in Egypt is available.<sup>26</sup>

Inadequacies in health data collection and dissemination in Egypt make it unlikely that information obtained on tuberculosis morbidity and mortality will be accurate.<sup>27</sup>

*M. tuberculosis* was identified as the etiologic organism in 19.7% of patients with infectious neurologic disease at the Abbassia Fever Hospital in Cairo, Egypt, from 1966 to 1989. This prevalence was second only to that of meningococci, and TB meningitis was the most frequent cause of death at this hospital.<sup>28</sup>

With an estimated TB incidence of 11 new cases per 100,000 people, Egypt has relatively low levels of TB according to 2005 data from the World Health Organization.<sup>29</sup>

The estimated annual risk of infection with TB has declined from 3.5% in 1952 to 0.24% in 2006, meaning that nearly 24 patients per 100,000 get the disease every year and 11 out of those 24 are sputum smear positive.<sup>30</sup>

Every year, the National Tuberculosis Control Program of the Ministry of Health and Population (MOHP) registers over 12,000 new TB patients; more than 50% of the cases are sputum smear-positive pulmonary TB. On the basis of an annual

risk of infection of 0.32%, it is estimated that about 8,000 people receive a diagnosis of TB at facilities other than those of MOHP.<sup>31</sup>

Although Egypt has an intermediate level of incidence and mortality (24 and 3 per 100,000 populations respectively), 66% of TB cases occur among the socially and economically productive age groups of 15 to 54 years. The latest surveillance data obtained in 2006 reveals that, the national population in Egypt is: 71,348,000 and Prevalence rate of TB is 35/100,000 of the population. Multi-drug resistant TB is 2.2 % of the new cases & 38.4 % among re-treatment cases according to a national survey in 2002.<sup>2</sup>

In this locality, a study made by Zaghloul<sup>32</sup>, included 100 cases (86 of them were suspected and 14 were diagnosed as TB). Age distribution of tuberculous cases (17) represented 23.5% for age 20-30 followed by 17.7% for each of ages 1-10, 30-40, 40-50 & >60 years. In contrary, age group 10-20 & 50-60 was zero percent and 5.9% respectively. Regarding sex; males represented 76.5% while females represented 23.5%. Regarding occupation, among tuberculous cases, workers and non-employed persons constituted 29.4% for each followed by professional (23.53%), then farmers (11.76%) and house wives (5.88%). There was a statistically highly significant increase of rural residence (76.47%) over urban residence (23.53%).

Another study made by Dawood<sup>33</sup>, searched for renal tuberculosis. The study included 60 cases (35 of them were suspected to be urinary tuberculosis "Group I" and 25 were under anti-tuberculous therapy "Group II") and 20 control "Group III". The most frequent age ranged from 20 to 30 years (31.6%) followed by age group from 30-40 years (26.6%), the age group from 40-50 and 50-60 years represent (15%) for each age. The last frequent ages range were >60 and 10-20 years represent 5% and 6.6% respectively. Male frequency (63.3%) was higher than female frequency (36.7%). The most common presenting complaints were dysuria (86.7%), renal colic (61.7%) urinary frequency (56.7%), positive past history of urinary TB (46.7%), loss of weight (28.3%), hematuria and fever (26.7% for each), loss of appetite (25%), night sweating (15%), kidney transplantation (6.7%), infertility and past history of pulmonary TB (3.3% for each).

Tuberculosis in renal transplant recipient is a serious problem which has high morbidity and increased mortality.<sup>34</sup> In Egypt, the incidence of TB among 700 kidney recipients in urology and nephrology center in Mansoura University were 4% and this was considered high compared to other areas.<sup>35</sup>

In Mansoura, Egypt a 5 years study (1998 – 2003) included 3790 specimens from different sites of the body suspected to have TB (sputum, urine, semen, endometrial biopsy, pleural fluid, pus, CS etc.) was performed, the patient's age ranged from 3 to 70 years (male represent 64% and females 36%). The most frequent cases were young adults. The results revealed TB cases in 6.2%. Positive samples for TB were 9.6% in sputum, 4.2% in urine, 3.1% in semen and 8.6% in endometrial biopsies, while other body fluids were negative for TB.<sup>15</sup>

### Tuberculosis control in Egypt

The incidence and prevalence of tuberculosis in Egypt has been declining due to increased efforts of the MOHP. Prevalence dropped from 88/100,000 population in 1990 to 24 in 2008, while incidence dropped from 34 in 1990 to 19 in 2008 according to data from WHO.<sup>36</sup>

Tuberculosis control in Egypt is carried out through 111 chest centers and 39 chest disease hospitals with 6351 hospital beds. Tuberculosis control activities are integrated through the primary health care system. The health staff working in these units is highly qualified due to the sustainable plan of human resource development. The WHO Directly Observed Treatment strategy (DOTs) was implemented starting from 1996 and became available to all patients in MOHP chest clinics by August 2000.<sup>30</sup>

The World Health Organization strongly advocates the use of directly observed therapy, short course (DOTs) elsewhere for drug-sensitive cases. This simple procedure means that the patient must be seen to swallow their medication under the eye of a trained (not necessarily medically) supervisor. Along with the proper prescription of drugs, WHO believes that DOT monitoring, which ensures that patients take the prescribed medications for the appropriate periods of time, will greatly reduce drug resistant TB.<sup>30</sup>

Egypt is classified as one of the 36 worldwide countries having achieved the global targets in both case detection and treatment success under DOTS.<sup>11</sup> In 2008, the case detection rate of positive cases in Egypt was 78% (global target is 70%) and treatment success rate was 89% (global target is 85%) (Ministry of Health and Population, 2010).

Treatment failure is a serious problem facing some national tuberculosis control programs. Significant risk factors for treatment failure in Egypt were irregularity of treatment non-compliance to treatment, deficient health education to the patient, poor patient knowledge regarding the disease and diabetes mellitus as co-morbid condition. In Egypt, treatment failure accounts for 3%–5% of the treatment outcome of new smear positive cases and 13%–17% of re-treated cases.<sup>37</sup>

Drug-resistant strains of *M. tuberculosis* pose serious public health problems. Multiple drug resistance and low cure rates are the most important problems facing TB control efforts in Egypt. There is a little information regarding the distribution of strains and the development of drug resistance, particularly in major population regions outside the immediate vicinity of Cairo.<sup>38</sup>

The development of drug resistance in the population has increased the possibility that TB may once again become an incurable disease.<sup>18</sup> Resistance to drugs is due to particular genomic mutations in specific genes of MTB. To date, nine genes are known to be linked to resistance to first-line anti-TB drugs; *katG*, *inhA*, *aphC*, and *kasA* for INH resistance, *rpoB* for RIF resistance, *rpsL* and *rrs* for streptomycin resistance, *embB* for EMB resistance, and *pncA* for pyrazinamide resistance. Resistance to multiple drugs is the consequence of an accumulation of mutations.<sup>39</sup>

In Mansoura the rate of drug resistance was 32.7%, with a higher prevalence of resistance in patients who had received previous anti-tuberculous treatment (70 %) than new patients (30%), according to the study which was carried out on 153 tuberculous patients (83 males and 70 females) with positive Bactec 460 culture for acid fast bacilli. Those patients were selected from Mansoura University Hospitals and Mansoura Chest Hospital. Genotypic analysis was done for

rifampicin resistant specimens and INH resistant specimens to detect mutations responsible for drug resistance by PCR amplification of *rpoB* gene for rifampicin resistant cases and *KatG* gene for isoniazid resistant cases. Finally, DNA sequencing was done for detection of mutation within *rpoB* and *KatG* genes. Genotypic analysis of RIF resistant cases revealed that 86.9% of RIF resistance were having *rpoB* gene mutation versus 13.1% having no mutation with a high statistical significant difference between them. Direct sequencing of *KatG* gene revealed point mutation in 92.3% and the remaining 7.7% had wild type *KatG* i.e. no evidence of mutation with a high statistical significant difference between them.<sup>40</sup>

According to Badran, 2007 drug resistance of TB is higher among rural residence than urban residence. INH shows the highest resistance, followed by rifampicin and ethambutol. The lowest resistance is for streptomycin.

## CONCLUSION

Although Egypt is not on the WHO list of 22 high-TB-burden countries, it is considered one of the high-burden countries in WHO's Eastern Mediterranean region, where TB constitutes the second most important public health problem after schistosomiasis.

The incidence and prevalence of tuberculosis in Egypt has been declining due to increased efforts of the MOHP. Prevalence dropped from 88/100,000 population in 1990 to 24 in 2008, while incidence dropped from 34 in 1990 to 19 in 2008 according to data from WHO.

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