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AIMS AND SCOPE:

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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Laboratories play an important role in the National Tuberculosis (TB) management and prevention programmes, particularly in the detection of TB cases, thus ensuring effective treatment and cure by periodic examination of sputum specimens by smear microscopy. Smear microscopy is a simple and inexpensive, yet highly sensitive tool in HIV negative cases compared to other relatively more expensive molecular biology procedures that are in vogue for detecting the disease among low burden non-endemic countries. To ensure its reliability, quality assurance apart from improvement and networking of laboratories at various levels is imperative. In addition, good quality culture & Drug Sensitivity Testing (DST) laboratories are needed to evaluate the level of drug resistance in the Region.

The SAARC TB Reference Laboratory was established with the support of the SAARC Canada Regional TB and HIV/AIDS project. One of the important components of this project was to improve the accuracy of laboratory diagnosis of respective National TB Reference Laboratories of the Region. To enable this, the SAARC TB Reference Laboratory is required to develop its capability by improving the basic infrastructure for networking all the National TB Reference Laboratories and undertaking external quality assessment programmes (EQAP) among the National TB Reference Laboratories of the Member States.

SAARC TB Reference Laboratory is involved in the panel testing scheme of Gauting Supranational TB Reference Laboratory, Germany for smear microscopy, culture and DST since 2008. Participation in the panel testing has helped to maintain the proficiency of the laboratory staff in smear microscopy, which in the long run would strengthen the SAARC TB Reference Laboratory to be able to function as the Supranational Reference Region. Similarly, the technical Staff from Gauting Supranational TB Reference Laboratory frequently visit the SAARC TB Reference Laboratory for providing feedback for further upgrade. The Centre monitors and coordinates activities pertaining to prevention and control of TB in the Region through the NTPs of the Member States. SAARC TB Reference Laboratory is currently working to strengthen and support the National Reference TB Laboratories of Member States in the area of external quality assurance of sputum smear microscopy (EQASSM), Culture & DST and also to implement international bio-safety norms in laboratory procedures.

SAARC TB Reference Laboratory has been conducting external quality assurance programmes of NTRL, annually since 2003. Since then STAC has been conducting 13 rounds of proficiency testing. Analysis of these reports revealed that except in 7th round (2010) which showed a major error (High False Negative) in one NTRL all other NTRLs have provided the acceptable performance achieving 90 to 100 percent performance.

In addition, SAARC TB Reference Laboratory conducts training programs for different categories of laboratory personnel, undertakes operational research studies for early diagnosis of TB and early detection of Multi Drug Resistant (MDR) TB. Further, efforts are proposed towards pursuing research of relevance, with international laboratories and research centers. These measures would enable strengthening the diagnostic services of NTPs and obtain reliable data on drug resistance prevalent in the Region.

There are 12 National Reference Laboratories and 69 Provincial/Intermediate Laboratories in the Region performing culture and DST for Mycobacterium tuberculosis currently and many more in the pipeline. Despite the extensive laboratory networks in the SAARC Member States, there are two Supra-national Reference laboratories in the Region currently which is the National Institute for Research in Tuberculosis (Formerly-Tuberculosis Research Centre), located in Chennai, and National Institute of Tuberculosis and Respiratory Diseases New Delhi, India to support their activities. Also, there is no Supra-national Reference Laboratory for HIV in the Region. Considering the geographical size, population and burden of TB, HIV and TB-HIV co-infection in the Region, there is an urgent need to upgrade the SAARC TB Reference Laboratory as a SAARC Regional Supra Reference Laboratory. To sustain and strengthen its current activities and to fulfill the felt demand of the Region, STAC Reference Laboratory, urgently requires strengthening of its Laboratory, to meet the internationally accepted Bio-safety norms.

This would also help to provide reference services for molecular diagnostics and conducting molecular research of public health importance. It will also help to regulate Bio-safety standard in the TB and HIV testing Laboratories in the Region. The Centre also has already established the required infrastructure to become a Supra Reference Laboratory for TB and HIV and has also proven TB DST accuracy and therefore accredited by the WHO SNRL, Germany. To extend the services of SAARC TB Reference Laboratory to the SAARC Region there is an urgent need for extension of its physical and technical facilities as a Supranational TB and HIV Reference Laboratory for this Region. Hence, all Member States of SAARC have been committed for this important Regional task.
SIDE EFFECTS ASSOCIATED WITH DRUGS USED IN TREATMENT OF MULTI DRUG RESISTANT TUBERCULOSIS AND TREATMENT RELATED FACTORS OF MULTI DRUG RESISTANT TUBERCULOSIS PATIENTS IN KATHMANDU VALLEY

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ABSTRACT

Introduction: Treatment of multi drug resistant Mycobacterium tuberculosis (MDR-TB) with second line drugs is associated with adverse drug reactions and toxicity. Aim of this study were to determine side effects associated with drugs used in treatment of multi drug resistant tuberculosis and treatment related factors of MDR-TB patients.

Methodology: A prospective study was carried out in National Tuberculosis Centre Bhaktapur Nepal. Questionnaires were used to collect data from patients.

Results: Total 101 MDR TB patients were included among them majorities were male (52%) and mean age of the patients was 31.2 years. Majority of patients (87.1%) had previous history of tuberculosis treatment and 54.5% were in intensive phase of treatment. The side effect associated with drugs used in treatment of MDR-TB reported by patients were joint pain (21.2%), nausea (20.3%), hearing disturbances (11%), gastrointestinal disturbance (9.9%), depression (9.6%), itching (8.1%), hypothyroidism (6.4%), dizziness (6.4%), seizures (3.8%) and hepatitis (3.5%). Last month 25.74% patients missed one or more doses of drugs and 3.9% missed drug doses due to side effect of drugs. Majorities of the patients used vehicle to reach health centre (92.07%), time to reach the health center (59.4%) were less than 30 minutes but majorities of patients (57.4%) were not satisfied by the counseling of health care worker.

Conclusion: The finding of this study shows that in MDR patients 12.8% were found new cases. Last month 3.9% patients were stopped the drugs due to side effects of drugs. Majority of patients (57.4%) were not satisfied by counseling of health care worker. Treatment of multi drug resistant tuberculosis with second line anti tubercular drugs is associated with side effects, health care worker counseling to MDR- TB patients with full attention is essential to encourage the patient’s moral and complete the treatment. Timely managing the side effects of medication is important in helping people to complete their treatment.

Key words: DOTS-plus, Mycobacterium tuberculosis, Second line anti tubercular drugs, Side effects.

INTRODUCTION

Tuberculosis (TB) is a major public health problem in Nepal. About 45 percent of the total population is infected with TB, of which 60 percent are adult. Every year, 45,000 people develop active TB, of whom 20,580 have infectious pulmonary disease. Treatment by Directly Observed Treatment Short course has significantly reduced the number of deaths; however 5,000 to 7,000 people still die per year from TB.¹ Directly Observed Treatment of Short Course - Plus is a part of DOTS program that adds approach for multidrug resistance tuberculosis diagnosis, management and treatment. Globally treatment outcomes for multidrug-resistant Mycobacterium tuberculosis remain poor and this is compounded by high drug toxicity.

Second line drugs are frequently associated with very high rates of unacceptable adverse drug reactions, needing frequent interruption and
change of regimen. Some authors reported that 41% patients experienced some side effects and only 21.1% patients required stoppage or change of drug in their study of 39 patients of MDR-TB. Close monitoring of the patients is necessary to ensure that the adverse effects of second line drugs are recognized quickly. The ability to monitor patients for adverse effects daily is one of the major advantages of Directly Observed Treatment as in category IV treatment running as a pilot project in some states of India. The majority of adverse effects are easy to recognize. Commonly, patients will volunteer that they are experiencing adverse effects. However, it is important to have a systematic method of patient interviewing since some patients may be reticent about reporting even severe adverse effects. Other patients may be distracted by one adverse effect and forget to tell the physician about others. The physician should be trained to screen patients regularly for symptoms of common adverse effects: rashes, gastrointestinal symptoms (nausea, vomiting, and diarrhea), psychiatric symptoms (psychosis, anxiety, depression, and suicidal ideation), jaundice, ototoxicity and peripheral neuropathy. Prompt evaluation, diagnosis and treatment of adverse effects are extremely important, even if the adverse effect is not particularly dangerous. If the adverse effect is mild and not dangerous like peripheral neuropathy, continuing the treatment regimen, with the help of ancillary drugs if needed, is often the best option. MDR-TB is a growing hazard to human health worldwide and threat to control of tuberculosis. Treatment of MDR-TB is difficult, complicated, much costlier, challenging and needs experience and skills. Reserve drugs are frequently associated with very high rates of unacceptable adverse drug reactions, needing frequent interruption and change of regimen. All measures should be taken to persuade and encourage patients not to stop treatment despite all its discomforts to prevent morbidity, mortality and transmission of MDR-TB. The aims of this study were to find out side effect associated with drugs used in MDR tuberculosis and treatment related factors of TB patients in Kathmandu valley.

**METHODOLOGY**

**Study Design**
A prospective study was carried out to DOTS-plus program of Kathmandu valley among multi drug resistant tuberculosis patients.

**Study Area**
The study was conducted in National Tuberculosis Center, Thimi, Bhaktapur Nepal from July 2012 to November, 2012.

**Study Population**
Patients who have multi-drug resistant tuberculosis and undergoing treatment through DOTS-plus programme in Kathmandu valley were included in this study.

**Inclusion and Exclusion Criteria**
Patients who have multi-drug resistant tuberculosis and undergoing treatment through DOTS-plus therapy for at least one and half month in the fiscal year 2011/12 and those who gave informed consent and willing to participate in the study were enrolled.

**Ethical Consideration**
Technical and ethical approval was taken from respective authorities to carry out this research work. Verbal informed consent was achieved prior to data collection from each patient who met the study inclusive criteria and briefly explained the aim of the study. Patient was assured to maintain strict confidentiality.

**Data Collection**
An interview was conducted to collect the data from the patients and questionnaire was adopted in this study. Patient name, age, TB history were rechecked immediately after interview by monitoring DOTS plus register. The interview was carried out in Nepali language.

**Data Analysis**
Data were coded and edited after which they were entered in datasheet created in SPSS Version 16.0. Cross checking was done to find out any mistaken entries in the spreadsheet. Data was presented by chart and diagrams.

**RESULTS**
It was found that majorities of the patients were male (52%) (Figure 1), intensive phase of treatment (54.5%) (Figure 2), and previous history of TB treatment (87.1%) (Figure 3) As reported by patients 25.74% had missed one or more doses of drugs and 11.5% missed four doses of drugs during last month (Figure 4). Last month 3.9% patients missed drug doses due to side effects of the drugs (Figure 5). Common side effect reported by patients were joint pain (21.2%), nausea (20.3%) hearing disturbances (11%), and gastrointestinal disturbance (9.9%) (Table1). Majorities of the

...
respondents used vehicle to reach health centre (99%), time to reach the health center (59.41%) was less than 30 minutes and waiting time (64.36%) was less than 15 minutes but majorities of patients (57.4%) were not satisfied by the counseling of health care work (Table 2).

<table>
<thead>
<tr>
<th>Side-effects</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint pain</td>
<td>21.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>20.3</td>
</tr>
<tr>
<td>Hearing disturbances</td>
<td>11.0</td>
</tr>
<tr>
<td>Gastrointestinal disturbance</td>
<td>9.9</td>
</tr>
<tr>
<td>Depression</td>
<td>9.6</td>
</tr>
<tr>
<td>Itching</td>
<td>8.1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>6.4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6.4</td>
</tr>
<tr>
<td>Seizures</td>
<td>3.8</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Table 1. Side effects reported by the patients (multiple response, n=89)

<table>
<thead>
<tr>
<th>Health system related factors</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convenience</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>59</td>
<td>58.42%</td>
</tr>
<tr>
<td>No</td>
<td>42</td>
<td>41.58%</td>
</tr>
<tr>
<td>Means of vehicle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On foot</td>
<td>8</td>
<td>7.9%</td>
</tr>
<tr>
<td>By vehicle</td>
<td>93</td>
<td>92.08%</td>
</tr>
<tr>
<td>Time to reach</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 min</td>
<td>60</td>
<td>59.41%</td>
</tr>
<tr>
<td>&gt;=30 min</td>
<td>41</td>
<td>40.6%</td>
</tr>
<tr>
<td>Waiting time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15 min</td>
<td>65</td>
<td>64.36%</td>
</tr>
<tr>
<td>&gt;=15 min</td>
<td>36</td>
<td>35.64%</td>
</tr>
<tr>
<td>Perception on waiting time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reasonable</td>
<td>75</td>
<td>74.26%</td>
</tr>
<tr>
<td>Not reasonable</td>
<td>26</td>
<td>25.74%</td>
</tr>
<tr>
<td>Counselling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>43</td>
<td>42.57%</td>
</tr>
<tr>
<td>No</td>
<td>58</td>
<td>57.43%</td>
</tr>
</tbody>
</table>
**DISCUSSION**

Multi drug resistant tuberculosis is defined as disease due to *Mycobacterium tuberculosis* that is resistant to isoniazid (H) and rifampicin (R), with or without resistance to other drugs. Primary drug resistance is defined as drug resistance in a patient who has not received any anti-tubercular treatment in the past, while acquired drug resistance is defined as resistance that develops in a patient who has received prior chemotherapy.\(^7\) Drug resistant TB is caused by inconsistent or partial treatment, when patients do not take all their drugs regularly for the required period because they start to feel better, and doctors and health workers prescribe the wrong treatment regimens or the drug supply is unreliable.

This study shows that male and female ratio is not statistically significant (1.1:1) and mean age of patient was 31.2 years. Majorities of MDR patient had previous history of TB treatment but 12.8% were new cases or primary drug resistant. This finding is consistent with the earlier study conducted by Singla *et al* in India found that mean age of MDR TB patient was 26 years and history of contact with tuberculosis patient 22% reported yes, 64% no and 14% not known.\(^8\) This finding suggests that TB is common among the economically active group having direct impact to the family and the national economy. This finding also supports the global burden of TB in developing countries where 75% of cases are within the economically and most productive age group (15-54years).\(^9\) This finding of the study also suggests that burden of TB will cause economic loss to the family and community in Nepal because it is found that an adult with TB, in the developing world loses on average 3-4 months of work time, 20%-30% of annual house hold income and 15 years income if patient dies causing staggering economic loss to the family and the community.\(^9\)

This study shows that side effects of drugs used in treatment of MDR tuberculosis reported by patients were joint pain (21.2%), nausea (20.3%), hearing disturbances (11%), gastrointestinal disturbance (9.9%), depression (9.6%), itching (8.1%), hypothyroidism (6.4%), dizziness (6.4%), seizures (3.8%) and hepatitis (3.5%). This finding is consistent with the earlier finding by Torun *et al*\(^11\) reported that one or more side effects developed in 182 cases (69.2%). These effects led the clinicians to withdraw one or more drugs from the treatment regimen in 146 cases (55.5%). Side effects observed most frequently included: ototoxicity (41.8%), psychiatric disorders (21.3%), gastrointestinal disturbance (14.0%), arthralgia (11.4%), epileptic seizures (9.9%), hepatitis (4.5%), and dermatological effects (4.5%). A study conducted by Singla *et al* in India shows that fifty-one (40%) patients had minor side effects that were manageable. However, 22 (18%) patients had major adverse reactions requiring removal of the offending drug(s) from the regime. Cycloserine produced major psychotic adverse reactions and had to be stopped in 15 patients. Kanamycin was the second most common drug to require interruption in five patients due to hearing loss and giddiness. International experience from five different initial DOTS-plus sites shows that only 2% of patients stopped treatment, but that 30% required removal of the offending drug(s) from the regimen due to adverse events.\(^12\) Managing major adverse reactions requires the help of specialist doctors and poses a challenge in resource poor countries. Anti-TB drug side effects are an inherent risk for patients commencing any type of anti-TB therapy, especially the drug-resistant cases. The Peruvian Ministry of Health has notified side-effects prevalence of 3.3% amongst treated patients.\(^13\) The emergence of side effects may depend on patients’ characteristics but also on concomitant events during therapy.\(^14\) Drugs associated with MDR-TB treatment is one of the most important factors associated with adverse reactions, increasing risk around 11 times compared to those who received first-line therapy. A prior study involving MDR-TB patients in Peru reported that 95% of treated patients had a type of adverse reaction to second-line TB drugs, with a proportion of 54% as toxic reactions.\(^15\) Others studies have found high prevalence (more than 50%) of adverse drug reactions among MDR-TB patients\(^16,11\) compared to the expected prevalence of mild reactions in those using first-line therapy (around 5–20%).\(^17\) In general, drugs for treating MDR-TB strains have greater toxicity effects and involve a long-term exposure (18 to 24 months), all in great contrast with the treatment of a sensitive strain of TB.\(^17\) Drug regimens for MDR-TB use agents in combination that are more toxic than the first-line drugs. Further, some anti-tuberculosis drugs used in second-line regimens for drug resistant tuberculosis also potentiate the toxicity of other agents used in the regimen.\(^18\) Psychiatric adverse effects are known in the treatment of
tuberculosis and are associated with increased mortality and unfavourable prognosis.19

Majorities (92.07%) of the patients used vehicle to reach health centre, 59.4% of patients’ time to reach the health center was less than 30 minutes and 64.3% patients waiting time was less than 15 minutes. A study conducted by Moranker et al20 reported that regular treatment under DOTS is also influenced by the cost, related to the treatment, such as fees of health care providers, travel cost and opportunity costs. For obvious reasons it is a more important barrier for women, who are poor and if they lower status. The most important reason for defaulting was economic conditions of the TB patients-unstable, irregular employment, lack of family support when the TB patient stops earning due to his illness.21 A study carried out by Lee et al22 reported that the financial support of the family become important in the continuation phase and patients who had no financial support had thrice the risk for defaulting. Major factors influencing treatment interruption are access to treatment such as distance, cost of transport, time, waged lost, and quality of drugs, levels of knowledge about TB and flexibility for transfer to another facility.

Finding of this study shows that 25.74% patients had missed one or more doses of MDR-TB drugs. Patients who did not know the consequence of incomplete treatment might at any stage of treatment stop taking the drugs. This interruption results in emergence of drug resistance to anti-TB drug. Above finding of this study suggests that more emphasis should be given on teaching patients about consequences of incomplete treatment. The premature interruption of treatment represents a problem for patients, their families and those who care for them, and those responsible for TB programmes.

In this study majorities of the respondents (57.4%) were not satisfied by the counselling of health care worker. Health care workers role is vital to control tuberculosis. TB patients fully depend on their advice. Their minor mistake or careless creates major problems. Health workers should teach TB patients’ simple measures how to decrease the risk of transmitting TB, dose and side effects of medicine, and what is the consequence if drug doses are not completed. Health care worker properly counselling them their full attention is essential to encourage the patient moral and complete tuberculosis treatment.

CONCLUSION

The finding of this study shows that in MDR-TB patients 12.8% were found new cases or primary drug resistant. Last month 3.9% patients were stopped the drugs due to side effects of drugs and common side effects of drugs reported by patients were joint pain, nausea, hearing disturbance, gastrointestinal disturbance and depression. Majority of patients (57.4%) were not satisfied by counselling of health care worker. Treatment of multi-drug resistant tuberculosis with second line anti tubercular drugs is associated with side effects, health care worker counselling to MDR-TB patients with full attention is essential to encourage the patient’s moral and complete the treatment. Timely managing the side effects of medication is important in helping people to complete their treatment.

REFERENCES


PERFORMANCE OF XPERT MTB/RIF ASSAY FOR DETECTION OF M.TB IN PULMONARY AND EXTRA-PULMONARY SAMPLES IN INDIAN PATIENTS

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ABSTRACT

Introduction: Conventional methods like Ziehl-Neelsen (ZN) staining and liquid culture have been the mainstay for diagnosis of Tuberculosis (TB). The gold standard Liquid Culture method has a longer turn-around time. In the wake of the TB catastrophe, newer rapid and easily accessible methods of detection are the need of the hour. A molecular method like the Xpert MTB/RIF assay has revolutionized the early and rapid diagnosis of TB. Objective of the current study was to assess the performance and utility of Xpert MTB/RIF assay for the diagnosis of M. tuberculosis in pulmonary and extra-pulmonary clinical specimens in a large Indian reference laboratory.

Methodology: The reference methods used were MGIT Liquid Culture system and ZN smear microscopy. Our study was performed in Global Reference Laboratory, Metropolis Healthcare, Mumbai, India for a period of 18 months with consecutive one thousand and forty two (518 Pulmonary + 524 extra-pulmonary specimens) clinical specimens obtained from the patients with clinical suspicion of tuberculosis. Diagnostic performance (sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the three methods were calculated with standard formulae.

Results: In comparison to MGIT Liquid culture, sensitivity of Xpert MTB/RIF assay for pulmonary and extra pulmonary specimens were 87.18% and 68.92%, respectively while in comparison to ZN smear microscopy the sensitivity of Xpert MTB/RIF assay for pulmonary and extra pulmonary specimens were 92.67% and 83.81%, respectively.

Conclusion: Our study concludes that in combination with the MGIT culture, Xpert MTB/RIF assay will significantly improve the detection rate of MTB bacteria.

Key words: Mycobacterium tuberculosis; Pulmonary; Extra-pulmonary; Xpert MTB/RIF assay, ZN staining

INTRODUCTION

Tuberculosis (TB) is a global public-health issue aggravated by the emergence of drug resistance strains. After Acquired Immuno deficiency Syndrome (AIDS), TB is the greatest killer of human population due to a single infectious agent M. Tuberculosis. Morbidity and Mortality from TB have been counted the highest from Low- and Middle-income countries. The African Region had 28% of the world’s cases in 2014, but the most severe burden relative to population: 281 cases for every 100,000 people, more than double the global average of 133.

India is under the world’s largest burden of tuberculosis (TB), accounting for one-fifth (24%) of the global TB incidence. The global annual incidence estimate is 8.8 million cases, of which 1.5 million cases are from India. Another issue faced by developing countries like India, is the emergence of drug resistant tuberculosis (DR-TB) particularly multidrug resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB). The disease usually affects the lungs (pulmonary TB). Extra-pulmonary TB is defined as TB affecting other sites of the body.
Recommended treatment for drug-susceptible TB is the combined use of first-line drugs; isoniazid, rifampicin, ethambutol and pyrazinamide for a period of six-months. Isoniazid and rifampicin are the powerful anti-TB drugs. TB bacteria resistant to isoniazid and rifampicin are indicative of multi-drug resistant tuberculosis (MDR-TB). Treatment for MDR-TB is comparatively longer and includes second line anti-TB drugs. Rifampicin resistance is a surrogate marker for MDR-TB.

Early rapid diagnosis of tuberculosis and appropriate use of recommended therapy is essential to control the emergence and spread of MDR and/or XDR strains. Conventional Acid-Fast Bacilli (AFB) smear microscopy by Ziehl-Neelsen (ZN) staining is a cost-effective method for the rapid identification of highly communicable TB patients. However, it is reported to be less sensitive as compared to the culture method. It gives no information about antibiotic resistance, viability and identification of the bacilli. Large MTB bacilli loads (10^5/ml) are required for a positive smear result. Culture medium is considered as the "gold standard" for TB diagnosis. It is more sensitive method than smear microscopy, detecting lower mycobacterial loads, for species identification. Accurate detection of TB bacilli and drug susceptibility can also be performed by culture method. However, longer time taken for detection of TB bacilli and species identification is its major constraint for routine TB diagnosis.

A molecular method, the Xpert® MTB/RIF assay (Cepheid, USA), was endorsed in 2010 by the World Health Organization (WHO), for the rapid identification of M. tuberculosis and antibiotic resistance in clinical specimens. The Xpert MTB/RIF is a rapid molecular biology gene based assay that fully automates sample processing, DNA amplification and detection. It performs a real-time-PCR reaction within a single closed cartridge. It requires very short hands-on time (<2hours) and can be performed by operators with minimum technical expertise. Revised National Tuberculosis Control Program (RNTCP) is a state-run tuberculosis control, an initiative of the Government of India. Post-completion of feasibility study, RNTCP has endorsed the policy of prioritizing to offer rapid molecular test Xpert MTB/RIF (CBNNAT) to all presumptive TB cases for early diagnosis of TB as well as Rifampicin resistance. Introduction of Xpert MTB/RIF assay has revolutionized the diagnosis of tuberculosis (TB) by simultaneously detecting the bacteria and resistance to rifampicin (rif), a marker for multi-drug resistant TB (MDR-TB) as well as one of the principal first-line anti-tuberculosis drugs.

The aim of this study was to determine the sensitivity and specificity of the Xpert MTB/RIF assay for the diagnosis of MTB in pulmonary and extra-pulmonary clinical specimens registered at Global Reference Laboratory, Metropolis Healthcare, Mumbai, India. The results obtained by the Xpert MTB/RIF assay and ZN smear were compared with the results obtained by MGIT liquid culture.

**METHODOLOGY**

1. **Study population and samples:**

This study was carried out at Global Reference Laboratory, Metropolis Healthcare, Mumbai, India for a period of 18 months from June-2014 through December-2015. In our study, consecutive one thousand and forty two (1042) clinical specimens obtained from the patients with clinical suspicion of tuberculosis were included. The number of male (557) and female (485) subjects were included in the study. Age (years) range of male was 9 to 91 years, whereas that of female was 01 month to 87 years. Average age of the subjects in the study was 39.52 years.

Inclusion criteria:
- Patients with clinical suspicion of tuberculosis
- Patient should be able to give at least their clinical history
- At least, the specimen material should be 3ml for expectorated sputum sample
- At least, 3ml sample volume for any kind of body fluids
- At least of 1cm X 1cm of tissue specimen

Exclusion criteria:
- Patients provided insufficient sample volume.
- Samples received without request of all three tests.

Follow up samples were not included in this study.

The collected clinical specimens (1042) comprised of pulmonary (518) and extra-pulmonary (524) specimens. The types of extra...
pulmonary specimens included Pus, abscess and aspirates, Body fluids (pleural fluids, ascitic fluids, cerebrospinal fluid, synovial fluid, urine and gastric fluids), Endometrium tissue, Lymph Node tissue, Spinal tissue and Bone Biopsy. The minimum volumes of sample required were as follows: 3 ml for expectorated sputum sample, 3ml for any kind of body fluids and 1cm X 1cm of tissue specimen. The sample was divided into 3 parts. Two parts were assigned to 2 different technologists, one in the Mycobacteriology laboratory, where the technologist read smears and inoculated cultures, and the other part in the molecular research laboratory, where the technologist performed the Xpert MTB/RIF assay, thus blinding the technologists to the results of other tests. The third part was stored at 2°C to 8°C for rechecking and reanalysis, if required.

2. ZN smear and MGIT culture:

The samples were processed for digestion and decontamination using 4% N-acetyl-L-cysteine and sodium hydroxide (NALC-NAOH) by the modified Petroff method14 and centrifuged. The speed of centrifuge was 3800 rpm and time of centrifuge was 15 mins, after decontamination. After centrifugation, the sediment was re-suspended in 1.0 to 1.5 ml of sterile phosphate buffer (pH 6.8). The Mycobacteria Growth Indicator Tube (MGIT) manual mentioned an addition of 1.0 to 2.0ml as re-suspending volume of phosphate buffer. This suspension was used for inoculation and cultivation in liquid medium culture system MGIT [mycobacteria growth indicator tube] Bactec 960 culture; BD Microbiology Systems, USA. The volume of re-suspended sample used for MGIT was 0.5 ml and the volume used for LJ culture was 0.1 ml. The tubes were incubated in the MGIT 960 instrument at 37°C. The specimens were also analysed by light microscopy after ZiehlNeelsen (ZN) staining of smear to investigate the presence of acid fast bacilli. The smear was checked for acid-fast bacilli under oil immersion and reported according to the Revised National Tuberculosis Control Program (RNTCP laboratory module).11 Solid culture was used only as backup and results were not separately analysed.

3. Xpert MTB/RIF assay:

The Xpert MTB/RIF assay was performed as described by Boehme et al.12 Sample reagent (SR) buffer was added (2:1 ratio) to all the unprocessed test specimens in 15 ml falcon tube and the tube was manually agitated twice during a 15 minute incubation period at room temperature. Then, 2 ml of the reaction material was transferred to the test cartridge by a sterile disposable pipette (provided with kits). Cartridges were loaded in the GeneXpert device and the automatically generated results were obtained after 114 min. The interpretation of data from Xpert MTB/RIF assay was software based and not user dependent. The result was obtained in a simple text format which could be read easily. In cases where results were reported as being invalid, no result or error, the sample was reprocessed and rerun when sufficient material was available. Samples with insufficient material for reprocessing were not included in the study. For this study, samples were sufficient for rerun in all such cases.

4. Statistical analysis:

Diagnostic performance (sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the three methods were calculated with standard formulae. When results were indeterminate and a sufficient amount of the sample remained, the assay was repeated once, and the second result was used for analysis. A negative result for smear microscopy was reported if no acid-fast bacilli were detected in at least 200 observation fields. Cultures in MGIT liquid media were judged to have a negative result if no mycobacterial growth was seen until 6 weeks after incubation. A tuberculosis negative result for the Xpert MTB/RIF assay was generated automatically following an interpretative algorithm with the Gene Xpert Dx software. Apart from calculating binary (positive, negative) variables for all the test outcomes, the results were processed to analyse them quantitatively.

RESULTS

Our study evaluated the diagnostic accuracy of Xpert MTB/RIF assay both for pulmonary and Extra-pulmonary TB cases and compared it with the conventional techniques. Out of the 1042 samples analysed in our study, 454 samples (43.57%) were Xpert positive which included 341 (75.11%) ZN smear positive and 113 (24.88%) Zn smear negative cases. Whereas, culture positive cases accounted for 451 (43.28%) ZN smear positive and 146 (32.37%) Zn smear negative entries (Table 1).
Table 1. Comparison between ZN smear microscopy and Xpert MTB/RIF assay

<table>
<thead>
<tr>
<th>Pulmonary Specimens (N=518)</th>
<th>Extra Pulmonary Specimens (N=524)</th>
<th>Total Samples (N=1042)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear</td>
<td>Smear</td>
<td>Smear</td>
</tr>
<tr>
<td>Pos</td>
<td>Neg</td>
<td>Pos</td>
</tr>
<tr>
<td>253</td>
<td>44</td>
<td>88</td>
</tr>
<tr>
<td>20</td>
<td>201</td>
<td>17</td>
</tr>
</tbody>
</table>

Sensitivity: 92.67%, 93.81%, 90.21%
Specificity: 82.04%, 83.53%, 82.98%
PPV: 85.19%, 56.05%, 75.11%
NPV: 90.95%, 95.37%, 93.71%

Our findings on the performance of the Xpert MTB/RIF assay corroborated well with studies regarding accurate detection of MTBC bacilli in AFB-negative specimens.17

Our study recorded 294 (28.21%) cases (235 pulmonary and 59 extra-pulmonary) which were smear positive, culture positive and Xpert MTB/RIF assay positive. This observation is in accordance with the studies carried out by Boehme et al (2011)18, Boehme et al (2010)12 and Helb D et al (2010).19

Using liquid culture as the gold standard for comparison, the overall sensitivity of Xpert MTB/RIF assay was 79.74% (87.18% for pulmonary specimens and 68.92% for extra-pulmonary specimens). The specificity of Xpert MTB/RIF assay was recorded at 86.25% (Table 2).

The results on the performance of Xpert MTB/RIF assay correlated well with previous studies20,21,22 and23 that report the sensitivity and specificity for pulmonary specimens ranging from 67 % to 90, and 94 % to 100 % respectively. The heterogeneity between studies may reflect differences between the patient population, patient selection, type of pulmonary and extra-pulmonary specimens and the quality of the samples.24

Our study also reported thirty one specimens that were smear positive but remained negative by Xpert MTB/RIF assay. Out of the 31 smear positive and Xpert MTB/RIF assay negative specimens, 19 of them were also negative for MTB culture. On the contrary, one hundred and thirteen specimens were not detected by smear, but were identified by Xpert MTB/RIF assay. Out of the 113 such cases, 80 cases were also detected positive by MGIT liquid culture while 33 cases remain undetected by MGIT liquid culture. This indicates superior sensitivity of Xpert MTB/RIF assay over ZN smears. Similar observations have been reported in studies by Scott et al (2011).25

Thirteen samples which remain undetected by both ZN smear microscopy and MGIT liquid culture were detected by Xpert MTB/RIF assay. Out of these 13 cases, 11 were extra-pulmonary and 02 were pulmonary samples. Thus, Xpert MTB/RIF assay detects cases which remain undetected by ZN smear and culture. In our study, only twelve specimens including pulmonary (05) and extra-pulmonary (07) were positive on culture and smear but negative on Xpert MTB/RIF assay. The reason for false negative Xpert MTB/RIF assay results may be due to the limited number of bacilli in those particular samples. Out of 12 cases, 03 cases grew Mycobacteria other than culture (MOTT) other than MTB complex in culture. The other 09 cases were smear positive but paucibacillary (scanty grading) and hence this could be the reason for negative Gene-xpert result. Also, it is possible that stressed bacilli in patients may grow in culture.
DISCUSSION

One of the most critical steps in tuberculosis management is the rapid and accurate laboratory diagnosis of *mycobacterium tuberculosis* (MTB) complex. It helps to achieve the most appropriate treatment strategy for TB. World Health Organization (WHO) recommended Xpert MTB/RIF assay as a point-of-care testing for TB bacilli. Xpert MTB/RIF assay is a rapid assay which provides diagnostic result for TB and RIF resistance within two hours. It is less prone to contamination; requires minimal biosafety facilities; can be performed by technicians with little training and no risk of laboratory cross-contamination because of its closed-cartridge design. Studies report a high sensitivity in smear-negative pulmonary TB which is particularly relevant for patients with HIV infection. The objective of our study was to determine the sensitivity and specificity of the Xpert MTB/RIF assay for the diagnosis of MTB in pulmonary and extra-pulmonary clinical specimens in comparison to MGIT liquid culture system and ZN smear microscopy. Published literature has suggested high sensitivity and specificity for Xpert MTB/RIF assay, primarily in smear positive specimens. The International Standards for Tuberculosis Care (ISTC) recommends that patients suspected of having pulmonary TB should submit at least two sputum specimens for bacteriological examination. One of these samples should be obtained early morning, because the sample would have the highest yield at that time. One of the reasons for low sensitivity of ZN smear microscopy is due to the fact that 10⁵/ml is required for AFB to be seen using smear microscopy. However it has been reported that multiple sputum tests can give a sensitivity of about 90%. The Xpert MTB/RIF assay is assumed to be specific; it only detects DNA from intact *M. tuberculosis* bacilli and contamination from free DNA is thought to be removed by a washing step. The assay, however, does not differentiate between viable, dormant, and non-viable intact *M. tuberculosis* bacilli that are shed during effective anti-tuberculosis treatment. In our findings—high rates of Xpert MTB/RIF assay positive results suggest that even DNA fragments from lysed or damaged bacteria could have been detected by Xpert MTB/RIF assay. This observation suggested that the Xpert MTB/RIF assay could be a complimentary test to culture for the diagnosis of TB. The paucibacillary nature of extra-pulmonary specimens with a tendency of *M. tuberculosis* to form clumps leads to an uneven distribution of the bacilli during cultures. Also, there is loss of viable bacilli during NALC-NaOH processing (due to decanting supernatant steps), unlike Xpert processing, wherein the entire volume of the processed specimen is used; and the Xpert sample reagent has a better homogenization and liquefaction efficiency than NALC-NaOH processing. Xpert MTB/RIF assay is a method with high specificity and false positive results may be explained by the detection of dead MTB that would not be detected on culture or the fact that this method has better sensitivity.

Xpert MTB/RIF assay detects both live and dead bacteria. False positive results may be explained by the detection of dead MTB that would not be detected on culture. Cross-contamination is known to be one of the reasons for false positive results. However, PCR in Xpert MTB/RIF is less prone to contamination due to the closed reaction chamber. Furthermore, the surfaces where the specimens are processed were extensively cleaned to avoid contamination with bacterial DNA. For reliable results a good quality of specimen collection is very important. A patient with a negative Xpert MTB/RIF result can still have TB.

The diagnostic accuracy of the Xpert MTB/RIF assay in the extra-pulmonary specimens couldn’t be analysed by specimen’s origin due to lack of adequate number of specimens. Also, definitive diagnosis becomes difficult due to paucibacillary nature of TB bacilli in extra-pulmonary specimens. In the present study, the combined sensitivity of Xpert MTB/RIF assay was 88.14%. A systematic review and meta-analyses conducted by Denkingeret al. showed that Xpert MTB/RIF assay has a sensitivity ranging from 50% to 100% with pooled sensitivity of 83%. More recently, Penzet al. reviewed 36 studies in their meta-analyses and confirmed Xpert MTB/RIF assay pooled sensitivity of 87% that is similar to our study. However, the sensitivity of Xpert MTB/RIF assay in the current study is lower than what was found in similar study by Ligthelm et al (sensitivity, 96.7%).
Limitations

Our study was conducted retrospectively and hence the results could not be correlated with radiological findings and histo-pathological reports. The sensitivity and specificity of MTB/RIF assay to detect Rifampicin resistance in our study could not be evaluated in our study as Rifampicin sensitivity by phenotypic method was not performed for all the positive samples.

CONCLUSION

Conventional methods like ZN smear microscopy and culture are laborious and require more time to establish clinical diagnosis of tuberculosis. Though the sensitivity of microscopy can be increased, still a large fraction remains undetected for TB. Several efforts are carried out to expand the coverage area of Xpert MTB/RIF assay usage across the world. Grants and subsidies are being provided by Government’s and various organizations to enable the availability of Xpert MTB/Rif assay in developing and underdeveloped nations where healthcare systems face economic constraints. Our study concluded that the Xpert MTB/RIF assay displays better sensitivity than ZN smears for early detection of MTB infection. However, the Xpert MTB/RIF assay results must always be confirmed by MGIT liquid culture. In combination with the MGIT culture, Xpert MTB/Rif assay will definitely improve the detection rate of MTB bacteria. This will ensure an overall increase in the detection rate and better sensitivity for diagnosis of MTB.

Conflict of Interest: We, the authors declare no conflicts of interest.

REFERENCES


THE PSYCHOSOCIAL CHALLENGES FACING MULTI DRUG RESISTANCE TUBERCULOSIS PATIENTS: A QUALITATIVE STUDY

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ABSTRACT

Background: The treatment for MDR-TB characterized by rigorous treatment regimen for long duration, higher incidence of adverse side effects, lower cure rate, and high treatment costs. This could lead to number of psychosocial problems that influence treatment adherence. MDR-TB patients registered under DOTS Plus programme during the period of 2013-2014 in Chennai and Madurai districts, of Tamilnadu were included for this study.

Objective: To understand the psychosocial issues facing MDR-TB patients, who are diagnosed and registered for treatment under DOTS plus programme.

Methodology: This study used Focus Group Discussions with people with MDR-TB. Focus Group Discussions were focused on physical, psychological, social and economical challenges which MDR-TB patients faced during their treatment.

Results: Most of the study participants did not disclose their TB status, even to their family members. The majority of patients were not aware of the diagnosis of MDR-TB and long duration of treatment. Stigma from family, community and health providers has been experienced by the majority of patients. Patients and their families were afraid of losing economic stability which was already precarious owing to the disease. This fear has often generated a great deal of stress.

Conclusion: Study finding indicates that there is a significant psychological, social, and financial impact of MDR-TB that has a direct impact on quality of life of MDR-TB patients and their families. There is a need for psychosocial intervention model (strategies) for MDR-TB patients and their caregivers to mitigate the negative effects.

Key words: Tuberculosis, Multi Drug Resistant Tuberculosis (MDR-TB), Psychosocial Issues, Stigma, Economic Impact

INTRODUCTION

Multidrug resistant tuberculosis (MDR-TB) is defined as resistance to, at least, rifampicin and isoniazid, the two most powerful first-line anti-TB drugs. Globally, the proportion\textsuperscript{1} of new cases with multidrug-resistant TB (MDR-TB) was 3.5% in the year 2013. Drug resistance surveillance data show that an estimated 480,000 people developed MDR-TB in 2013 of which 210,000 people died. Treatment outcomes of MDR-TB documented a success rate of 48%, death 16%, interrupted treatment 24% and failure 12%.\textsuperscript{2} In India, the available information from the several drug resistance surveillance studies suggests that the prevalence of MDR-TB is 2–3% among new cases and 12-17% among re-infection cases.\textsuperscript{3} It was estimated that out of 73,000 MDR-TB patients living in India, only 1,660 cases were notified and 1,136 cases (1.6%) were put on treatment.\textsuperscript{4}

The treatment for MDR-TB characterised by rigorous treatment regimen for long duration, higher incidence of adverse side effects, lower cure rate, and high treatment costs.\textsuperscript{5} This could
lead to number of psychosocial problems that influence treatment adherence. Recognising these problems associated with MDR–TB, ‘DOTS Plus’ guideline developed by the Ministry of Health and Family Welfare, Government of India recommends for an integrated approach to treat this disease. DOTS Plus strategy, consists of a multidisciplinary team of providers which includes physicians, nurses, social workers, community health workers and volunteers who provide a range of services for the MDR-TB patients including psycho social and community support. While several studies in India and other countries have investigated psychosocial problems associated with TB patients, still there is a dearth of studies among MDR-TB patients in the same context. The present study was undertaken to explore and understand the psychosocial issues that negatively impact the treatment adherence among MDR-TB patients, who have been diagnosed and registered for treatment under RNTCP.

**METHODOLOGY**

This qualitative study utilized FGDs and interviews covering 83 (68 MDR-TB patients and 15 HCW) participants diagnosed as MDR-TB patients and registered under the DOTS Plus programme between the fourth quarter of 2013 and first quarter of 2014.

Patients who expressed willingness and given informed written consent were invited to participate in FGDs. Each FGD comprised of six to eight members both male and female. Care was taken to maximize the comfort levels of patients. FGDs generally coincided with patients drug collection day and they were offered sum of Rs. 100/- ($ 1.8 at the time of the study) to meet their food and local travel expenses.

**Study instruments**

A qualitative FGD guide was prepared based on the literature review and previously gained experience by the team (Box-1). The thematic areas in the guidelines included the MDR-TB patient’s physical problems (pain, breathlessness, tired, dizziness, feeling sleepy), psychological disturbances (worries, fear, tension, denial, depression), social problems (disclosure issues, rejection, enacted stigma, perceived stigma, discrimination by family members, community) and economic problems (inability to go for work, work absenteeism, loss of income, borrowings). In addition, challenges they faced during treatment and further to lead normal life were covered.

**Data analysis**

All FGD sessions were audio recorded and the audio taped information were transcribed verbatim in Tamil and translated into English. Transcribed and translated qualitative data were entered in NVIVO software programme.

**Box 1. Sample focus group discussion questions**

- Have you disclosed your MDR-TB status to anyone?
- Have you had any problems with regard to disclosure of your MDR-TB status?
- What was your reaction to diagnosis of MDR-TB?
- Reactions of your family members after you were diagnosed as MDR-TB?
- Have you experienced any discrimination on account of illness?
- What do you think are the reasons for you getting MDR-TB?
- Could you elaborate your perception & problems you have encountered because of MDR-TB?
- Can you describe the economic problems faced due to MDR-TB illness?
- Do you have any concerns about future with MDR-TB illness?
- What might be some of the intervention strategies that would be acceptable & feasible?

**Figure 1. Conceptual framework of MDR-TB and its psychological, social and economic impact**
Content analysis and theoretical thematic interpretation has been done involving both deductive (top down) and inductive (bottom up) coding and linking codes. Based on the contextual psycho social themes which were identified in the analysis, a flow chart was developed (Figure-1). Transcribed data were divided into following five specific themes.

i) Knowledge about diagnosis of MDR-TB,
ii) Initial reaction to illness,
iii) Challenges related to disclosure issues
iv) Experience of stigma and
V) Economic problems faced by MDR-TB patients

Human subject protection

This study was approved by the Scientific Advisory Committee and Institutional Ethics Committee of NIRT, Chennai (IEC No. 2013004). Approval from Institutional Review Boards of GHTM, Tambaram, Chennai and Government Rajaji Hospital, Madurai was also obtained.

RESULTS

Profile of participants

Table 1. Socio-demographic profile of participants

<table>
<thead>
<tr>
<th>Profile</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47</td>
<td>69</td>
</tr>
<tr>
<td>Female</td>
<td>21</td>
<td>31</td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmarried</td>
<td>08</td>
<td>12</td>
</tr>
<tr>
<td>Married</td>
<td>53</td>
<td>78</td>
</tr>
<tr>
<td>Widow / Widower</td>
<td>03</td>
<td>04</td>
</tr>
<tr>
<td>Separated</td>
<td>04</td>
<td>06</td>
</tr>
<tr>
<td>Educational Status</td>
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<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>08</td>
<td>12</td>
</tr>
<tr>
<td>Primary</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>Secondary</td>
<td>34</td>
<td>50</td>
</tr>
<tr>
<td>Higher Secondary</td>
<td>04</td>
<td>06</td>
</tr>
<tr>
<td>Degree and above</td>
<td>06</td>
<td>08</td>
</tr>
<tr>
<td>Occupational Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily Wage / Labour</td>
<td>18</td>
<td>26</td>
</tr>
<tr>
<td>Home maker</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Self employed</td>
<td>07</td>
<td>10</td>
</tr>
<tr>
<td>Service (Pvt. &amp; Govt.)</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>Agriculture</td>
<td>06</td>
<td>09</td>
</tr>
<tr>
<td>Unemployed</td>
<td>16</td>
<td>24</td>
</tr>
</tbody>
</table>

Focus Group Discussions conducted among a sample of 68 MDR-TB patients alone was analysed and results are described in the following pages.

Study participants were aged between 19–73 years, and more than half of them were married. With respect to education majority had school level education. Except one patient, all were started treatment under Category-II regimen in RNTCP, subsequently diagnosed as MDR-TB and placed under DOTS Plus Category-IV regimen. Participants were homogenous in terms of age in three out of five FGDs. Two FGDs comprised of slightly older participants. However, participants in all five FGDs were daily wage earners.

i) Knowledge about diagnosis of MDR-TB

One third of participants did not know their MDR TB status, reasons for MDR-TB and the need for prolong duration of treatment. Participants reported that they were affected with ‘muthina TB’ (advanced form of TB) and ‘Valarntha TB’ (over grown form of TB. Few others reported that health care providers told them to receive daily injections for six months, and on medication for 24 months. However participants felt that reasons for this was not explained to them. One male participant expressed that, “I was informed that I need to take 12 tablets per day for two years with 6 months injection daily, no one informed me that I have MDR TB” (Male-age 36 years)

ii) Initial reaction to illness

One of major issues brought out by the participants was fear. Participants both men and women had undergone fear of infecting other family members, fear of death and fear over future of family members.

On hearing about long duration of treatment and getting to know quantum of drugs to be consumed the participants internalised the problem dimension and undergone series of initial reactions. More than half participants felt guilty as they were told that this illness was due to their fault of being non adherent to TB treatment. “I am not able to swallow tablets and I feel it is very hard to take 12 tablets. I vomit one or two tablets. I feel drowsy; I even get unnecessary dreams and nightmares...” (Male-age 35 years)

One college going student (male-21 years) said that his perceived stigma did not allow him to...
concentrate on his studies. He stated that “I was not OK, I cried, I could not concentrate on my exams, at this young age I got this disease”

Other major issue brought out by the participants was fear. Most of the respondents (both men and women) underwent fear of infecting other family members, fear of death and fear over future of family members. The young patients were afraid of their marriage prospects. “I am already 24 years old female, now that I have MDR-TB, will I ever get married? I am worried about my future life”

Apart from fear, other psychological issues such as disbelief, denial and depression etc., were consistently reported by every participant in the FGDs. MDR-TB has impacted sexual life also. One female participant sacrificed her family life due to fear of infecting her spouse and she said the following. “I avoid sexual contact with my husband to prevent MDR-TB infection to him” (Female-age 21 years).

“I cried. I could not concentrate on my exams. At this young age I got this disease” (Male-19 years)

The experiences of depression made participants feel self-pity over his/her disease status and other problems related to the disease. Self blaming for all that happened was a choice for many. Once this condition worsens, suicidal ideation cropped in. Disbelief and denial often led to depression and suicidal thoughts. Some of the expression of denial and disbelief by the participants were “I felt like killing myself. How was I going to take tablets for two years? …..I do not even have proper food” (Male-36 years)

“I am willing to take two years of treatment. If I am not cured this time also there is no other way and I will have to die” (Female-29 years)

iii) Challenges related to disclosure issues

Majority of the participants expressed that they did not disclose their MDR-TB status to their family members, as disclosure of TB itself was presumed as a sensitive issue, leading to rejection within the home. As one young participant (Male-age 21 years), revealed his fear of future marriage prospects. “I feared to disclose MDR-TB status to my relatives especially to my aunt owing to fear of my future” (Male-age 21 years)

Another issue of disclosure was negative impact it might generate in the neighbourhood. One of the participants (male-35 years) had expressed that his neighbours have labelled him as ‘chronic sick person’. As a result he rarely moved out of his home to avoid facing uncomfortable questions from neighbours. “I am asked questions such as why I am so thin, why do I still have cough? why I am taking tablets?…. I seldom left my home to avoid answering such questions” (Male, 35 years).

“I am scared to mix with any one, not attending any social gathering ,not going out for any purposes and now I got used to stay alone in a separate room” (Male, 45 years).

iv) Experience of stigma

A common response among both men and women in the discussion was that MDR-TB patients faced discrimination from within and outside the home on account of prolonged treatment that required frequent visits to the hospital.

a) Discrimination within family

Most of the respondents reported that they faced discrimination within their family. This was reflected in abusive remarks either being sent out of the home or being isolated within the family. Few have opted to keep their belongings separate within the house. In many instances in-mates have neglected a MDR-TB patient altogether and considered him/her as a burden to their family. Household discrimination in particular, makes life very difficult for MDR-TB patients. It was expressed by a male participant. “I lost my parents. My brothers and sisters are not accepting me ever since they have heard that I have TB and need to continue treatment for two years. Now I am staying on the platform” (Male-31 years).

Sometimes patient’s family reacted favourably, which the patients long for. In some cases families ostracized the patient to a point of confining him/her to the most dirty and remote part of the house and limited any kind of interaction with him/her.

Half the participants reported that their friends and neighbours ill-treated and avoided them. Participants reported experience of heartedness both directly and indirectly. Some of them also reported adverse reaction from neighbours. Two
respondents reported that they were asked to vacate their house due to their illness. Many participants experienced discrimination in public places too. Two respondents were asked to vacate their house due to their persistent illness. Expression of two participants is narrated as “Soon after I was discharged from TB hospital, my house owner forced me to vacate the room. I was sleeping on platform” (Male-21 years)

“My neighbours keep asking me why I go to the hospital so often and make rude comments at my persistent symptoms of cough…” (Male-31 years).

This included questions as why do they (patients) make frequent visits to hospital, why they were sick “so long” etc., neighbours also made comment on their persistence cough. A male patient aged 35 years expressed self inhibition that made him stay in-door for long out of fear of discrimination. “Most of the times I never go out of my house because I could not face questions such as: why I am so thin?; why do I still have cough?; Why I am taking tablets? …………” (Male-35 years).

b) Discrimination by health provider

A common response among two third of participants was the discrimination from health care provider. Participants were made to feel disgraced and discriminated at the hands of health care workers. This was highly distressing to MDR-TB patients. Delay in health care centre, attitude of health staffs to them, loud comments about their illness and not allowing proximity to them were reported. Statements expressed by the participants about health care workers are, “I am treated differently as compared to other patients attending the health care centre. I was told to move away and sarcastic comments were made.” (Male - 34 years).

“When a health worker found difficult to give an injection, she scolded me rudely without any reason; because of this I was so upset and distressed…..” (Female - 29 years).

“A health worker visited my house and informed my mother that I was a MDR-TB patient; further she told her that MDR-TB is dangerous and advised her not to be close to me. My relationship with my mother was ruined” (Male-29 years).

v) Economic problems faced by MDR-TB patients

Often patients were the only working members of the household and most women had responsibility for running the home as well as taking care of children at home. Patients and their families were afraid of losing economic stability which was already precarious owing to disease. This fear has often, generated a great deal of stress. “I stopped going to work and stayed at home hence unable to contribute to household expenditures. My brothers and sisters used to visit me rarely and give sum of Rs. 200 to 300 and go off. I was financially affected as a result worried and felt guilty” (Male-35 years).

“I need to travel 4 to 5 kilometres daily for taking drugs. I am the bread winner of the family. I could not attend every day as I need to go for work. When I take tablets with injection I could not do any activities, I am unable to maintain regularity” (Male-31 years).

Patients from the rural areas have to travel 6-15 km to reach the treatment centre for drug collection and for receiving injection which costs them around Rs. 100 to 200. It was stated by a rural patient “If I visit hospital for treatment, I have to travel 15km from my village. I need at least Rs. 100 per visit to spent for bus ticket for me and my wife, we also have to drink a cup of tea, If I have money we will take lunch otherwise come home with hungry” (Male-49 years).

It was presumed that urban patients have more transportation, easy access to treatment centres which made it less expensive. Interestingly it was noted though the distance to treatment centre was less; patients have to change over at least two buses or take alternate mode of transport which made them spent considerable amount for travel.

During the MDR-TB treatment, patients reported to have experienced serious and life threatening complaints including breathlessness, gastroenteritis, severe cough for which they approached private clinics or private practitioners for timely relief. Such unexpected treatment episodes incurred higher cost to the patients and even pushed them to borrow money, further making them debt. It was reported by a patient (male-49 years) who had spent Rs 2,00,000 in a
private hospital in an urban locality over a period of six months. More than one third of the participants have expressed the need for financial or nutritional assistance during the treatment. This was narrated by a patient “I am the only earning member of the family, now I am unable to go to work and cannot provide money to run the family. I also need money to go for treatment. Any financial assistance provided during treatment and nutrition will be of great help” (Male, 45 years).

**DISCUSSION**

This study had highlighted multiple challenges faced by MDR-TB patients such as disclosure, stigma, psychological and economic problems. These findings corroborate the findings from other studies, which have highlighted the psychological, social and economic challenges experienced by MDR-TB patients. This result warrants a comprehensive intervention plan to address these issues in a phased manner in order to enhance treatment adherence and better quality of life among MDR-TB patients.

One of the salient findings from this study was lack of knowledge on diagnosis of MDR-TB among patients registered under the DOTS Plus programme. From the public health perspective, knowledge on illness is an important component which helps the individual to obtain, communicate, process, and understand basic health information. This highlights the need for imparting knowledge about MDR-TB among infected patients. Participants also reported that the health care workers have not informed them about MDR-TB. This may be due to the poor knowledge on MDR-TB among health care workers themselves. This was substantiated with the findings reported that only less than half of health care workers had correct knowledge on TB. Similarly another study among health care workers and TB patients conducted in Southern Nigeria noted that one third (38%) of health care workers and most of the TB patients (82%) had poor knowledge about of MDR-TB. It implies that there is a need for training and retraining health care workers on MDR-TB so that they can give appropriate health education for patients.

The present study found that MDR-TB patients have experienced stigma from their own family, community and health care system. The literature indicates that stigma, isolation, sense of social support, helpless feeling, and other psychological issues related to the disclosure of the diagnosis, adversely affect the TB treatment adherence. Moreover stigma also had its direct impact by affecting patients in multiple ways and it has been shown to hinder adherence to treatment. Utilizing principles of motivational interviewing which was found to be effective in improving treatment adherence in India, could be further explored among MDR-TB patients. In addition to educating to patients, their families and employers on MDR-TB it becomes important to help them (patients) understand their problems and help them to overcome both perceived and enacted social stigma.

It was found that both morbidity and treatment of MDR-TB produced an economically vulnerable situation for patients. Due to MDR-TB, many patients have experienced physical ailments related to their disease, such as shortness of breath, fatigue, or wasting, headaches, gastritis, depression and, peripheral neuropathy. These physical complaints diminished their ability to take-up productive work. In this study majority of the participants were from low socioeconomic status (wage labourers). They suffered an inability to work and were stressfully trying to overcome the feelings of ‘uselessness’ and being ‘a burden’ for their families. In addition TB itself limits the patient’s ability to purchase food, medications and obtaining relief from other stressors. It was estimated by WHO that in an average drug sensitive TB patient loses three to four months of work-time and up to 30% of their household annual earnings. The cost per patient treated for drug-susceptible TB in 2013 was in the range of US$ 100–US$ 500 and very high for MDR-TB ranged from an average of US$ 9235-US$ 48553. All these conditions have forced MDR-TB patients to borrow money from money lenders which caused more stress, isolation and depression. One alternate strategy is to provide health insurance coverage for TB patients (for in and outpatient costs) which could critically address the TB related financial hardship. We highlight Verena et al, who emphasised the severe impact of MDR-TB related costs on the household and advocated for the inclusion of TB services in national health insurance schemes supported by food and transport subsidies.
It was reported from Lima, Kazakhstan and Nepal that through psychosocial interventions treatment adherence to TB was improved. Similarly offering free treatment, hospital discounts, transportation stipends and psychosocial counselling based on the need assessment have improved treatment success. In Kazakhstan, ‘Psychosocial support program’ provided to MDR-TB patients was also successful in reducing default rates. In Nepal, an intervention which provided counselling support to MDR-TB patients showed that cure rate was 85%.

Suggested psychosocial intervention strategies

These findings highlight the need to apply an integrated intervention model that includes counselling and active health education in addition to incorporating successful experiences of generic models of service delivery. In this direction, the researchers have compiled and re-grouped the findings under three broad areas viz., psychological challenge, socio-economic challenge, and medication challenge. As a result, the researchers suggest an intervention model (please refer to Figure 2) that would alleviate sufferings experienced by MDR TB patients.

- Psychological support can be offered by either Medical social worker/counsellor or psychiatrist. One to one individual counselling session with psychologist or medical social worker could help in clarifying many of their doubts/fears and reducing their psycho social sufferings. Health education should be offered before initiating treatment as observed in this study.
- Socio-economic support in terms of monetary assistance, nutritional support can be offered to mitigate financial hardship experienced as a result of illness.
- Wherever feasible peer involvement can be promoted, peer participation strategies which was found successful in HIV prevention.
- Medication support can be explored from medicine to DOTSs provision. DOTS can be further simplified and arranged near to patient’s residence. Reduction in number of tablets perhaps fixed dose combination, change in health system (DOTS centre) functioning can also be explored.

Limitations of the study

This study was conducted among MDR-TB patients registered under DOTS Plus programme in government health facilities. Results produced from this research may be unique to the study setting in which we have conducted and may not be readily generalized to other settings. Furthermore we used qualitative tool to collect information for the purpose of this study which has its own limitations. However, our work highlights unexplored issues that are likely to be relevant to many developing countries with high MDR-TB burden, particularly those with a similar socioeconomic status.

CONCLUSION

This qualitative study has revealed significant psychological, social, and financial challenges associated with MDR-TB to patients and their families. There is a need for psychosocial support of MDR-TB patient and their caregivers to mitigate the negative effects of stigma, and to manage the associated psychological stressors. Our findings also raise several policy relevant issues in the management of MDR-TB in the community. There should be policy debates and reforms to innovate intervention strategies, which could aid the MDR-TB patients to cope with their psychosocial challenges leading to improved treatment adherence, reduced default and TB transmission rates. Besides this there is a critical need to examine the patients' financial concerns about higher treatment cost, transportation cost and loss of income.
REFERENCES


SO socio-demographic and clinical profile of hiv positive patients attending integrated counseling & testing centre of a primary health centre in delhi

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ABSTRACT

Introduction: The Human Immunodeficiency Virus (HIV) infection is a global pandemic affecting principally the sexually active and economically productive population of any country. Additionally the dual epidemic of HIV and TB infection is of growing concern in Asia, where nearly two-third of TB-infected individuals live and where tuberculosis now accounts for 40 percent of HIV/AIDS deaths. Keeping this in mind, a study was conducted to understand the profile of HIV/AIDS patients attending Integrated Counseling and Testing Center (ICTC) located at Primary Health Centre, Palam in Delhi.

Methodology: This was a descriptive record based study undertaken at ICTC, PHC PALAM, New Delhi. Records of all HIV seropositive patients identified in reference period (January 2010 to December 2014) were analyzed retrospectively to assess the socio-demographic and clinical profile including possible route of transmission, CD4 counts at the time of first reporting to the Anti Retroviral Treatment (ART) centre and the presence of co-infections including tuberculosis were recorded. Total 77 HIV seropositive patients were identified.

Results: Mean Age of presentation of male was 31.18 ± 8.85 years (12-60 years) and female 30.30 ± 10.07 years (7-53 years). Majority of HIV+ persons were married (16% of males and 6% females were unmarried). 24% of women were widows. Majority of HIV+ males and females had only primary schooling. 11% males and 21% females were illiterate. Main occupations of HIV+ males were daily wages labor and salaried service or other unspecified four out of 5 HIV+ women were housewives 70% of subjects were either referred from RNTCP or were self reporting. Heterosexual route was the most common route of transmission. Mean CD4 counts Males: 190.48 ± 180.52, Females: 286.21 ± 220.25 (t=2.09; p=0.039, significant). At the time of first reporting to ART centers, mean CD4 count was significantly higher in HIV+ females as compared to males. More than 50% of HIV+ males and 30% of females had co-infection of HIV & TB. CD4 count was associated with gender and co-infection with TB. Significantly higher odds of HIV-TB co-infection among male as compared to females (chi-square=4.49, p=0.034) and odds Ratio=2.76 (1.07 – 7.14).

Conclusions: Low literacy and some occupations carry higher risk of HIV. CD4 count was associated with gender and co-infection with TB. Odds of co-infection with TB were higher in males. Analysis of information at ICTC & ART centre should be used to monitor and plan HIV prevention and control in the area.

Key words: HIV, Tuberculosis, Socio-demographic profile, Clinical profile

INTRODUCTION

The Human Immunodeficiency Virus (HIV) infection is a global pandemic1 and a significant public health problem which has serious socio-economic and developmental consequences as it affects principally the sexually active and economically productive population of any country.2 Additionally the dual epidemic of HIV and TB infection is of growing concern in Asia, where nearly two-third of TB-infected individuals live and where tuberculosis now accounts for 40 percent of HIV/AIDS deaths. The overlap of TB-HIV co-infection with multidrug resistant TB (MDR) and extensively drug-resistant TB presents a substantial challenge and threatens to
curtail the progress in controlling TB and HIV/AIDS and in reducing the mortality associated with these diseases. Tuberculosis accounts for 1 in 4 of AIDS deaths globally and is amongst the commonest causes of morbidity in people living with HIV and AIDS (PLWHA). Currently, approximately 34 million people are infected with HIV, and of them at least one-third are co-infected with TB. Individuals co-infected with HIV and TB are 30 times more likely to progress to active tuberculosis. Tuberculosis infection enhances replication of HIV and can possibly hasten the progression of HIV infection to AIDS. HIV/AIDS and TB co-infection present special challenges to the expansion and efficacy of DOTS programs and the Stop TB Strategy. The lifetime risk of developing active tuberculosis in immunocompetent individuals has been estimated to be 5%–10% during the lifetime, however in HIV-positive patients this risk is increased by 5% to 15% annually.

The epidemiology and clinical presentation of the syndrome varies greatly across the globe. To enable planning of targeted interventions involving focus on high risk groups including female sex workers, men who have sex with men, injecting drug users (IDU), trans-gender, single male migrants and long distance truckers under National AIDS Control Program (NACP) in India, it is desirable to know the epidemiological pattern and clinical profile of the disease in a particular area. Keeping this in mind, a study was conducted to understand the profile of HIV/AIDS patients attending Integrated Counseling and Testing Center (ICTC) located at Primary Health Centre, Palam in Delhi.

**METHODOLOGY**

Under National AIDS Control Programme (NACP) in India, Integrated Counseling and Testing Centres (ICTC) have been set up to provide comprehensive services including testing for HIV infection for walk-in-clients as well as those referred from various healthcare facilities in Government sector, NGOs and private sector. Dedicated counselors and laboratory technicians posted at ICTC are trained at accredited institutions under the programme. Diagnostic kits of approved specifications are procured and supplied to ICTCs and stored at prescribed temperature. Even if a client visits a private facility for HIV testing, the client is retested for HIV at ICTC and confirmed for HIV infection based on algorithm prescribed under NACP. Thus data generated at ICTC have high level of validity with negligible element of bias or error. There is high level of cross-referrals between ICTCs and DOTS centres throughout the country as per NACP guidelines.

ICTCs are set up throughout Delhi at strategic locations for providing services to the catchment area. ICTC at Palam Primary Health Centre is the only testing centre under NACP in the catchment area which comprises of families from all sections of the society including nearby Dwarka, a large multi-rise residential sub-city. The services are free of cost for all clients, irrespective of socio-economic status. Confidentiality of clients and their HIV status is maintained with high level of integrity. As ICTCs are the gateway for free anti-retroviral treatment centres set up under NACP, these centres have high level of coverage and thus adequate level of representativeness.

This was a descriptive record based study conducted at Integrated Counseling and Testing Centre of primary health centre, Palam situated in New Delhi. All subjects who were identified to be HIV sero-positive during the reference period i.e. in between 1st January 2010 to 31st December 2014 were included. The socio-demographic and clinical profile was assessed with the help of a semi-structured proforma. Socio-demographic profile included identification characteristics, age in completed years, marital status, education and employment status. Clinical profile included possible route of transmission, CD4 counts at the time of first reporting to the Anti Retroviral Treatment (ART) centre and the presence of co-infections including tuberculosis.

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 18 and Epinfo. Qualitative data was expressed in proportions while mean and standard deviation were calculated for quantitative data. Student t-test and Chi square tests were used for comparing the characteristics of the study participants.

**RESULTS**

Total 77 subjects were identified to be HIV sero-positive out of which 44 were males and 33 were females including 6 pregnant women. Mean age of the study subjects was 31.18 ± 8.85 years (12-60 years) for males and 30.30 ± 10.07 years (7-53 years) for females. Nearly 59% of HIV+ males were in the age group of 25 to 34 years and one in four HIV+ females were in the age group of 15
Majority of the study subjects were married. Only 16% of males and 6% females were unmarried. Out of total females, 24% of women were widows.

Table 1. Profile of HIV positive persons detected at ICTC, Palam, Delhi: 2010-14

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Groups</th>
<th>Male (% =44)</th>
<th>Female (% =33)</th>
<th>Total (% =77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>&lt;15</td>
<td>2(4.5)</td>
<td>2(6.1)</td>
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</tr>
<tr>
<td></td>
<td>15 to 24</td>
<td>4(9.1)</td>
<td>8(24.2)</td>
<td>12(15.6)</td>
</tr>
<tr>
<td></td>
<td>25 to 34</td>
<td>26(59.1)</td>
<td>12(36.4)</td>
<td>38(49.4)</td>
</tr>
<tr>
<td></td>
<td>35 to 44</td>
<td>9(20.5)</td>
<td>7(21.2)</td>
<td>16(20.8)</td>
</tr>
<tr>
<td></td>
<td>45+</td>
<td>3(6.6)</td>
<td>4(12.1)</td>
<td>7(9.1)</td>
</tr>
<tr>
<td>Mean Age</td>
<td>31.18 ± 8.85</td>
<td>30.30 ± 10.07</td>
<td>30.8 ± 9.34</td>
<td></td>
</tr>
<tr>
<td>Marital Status</td>
<td>Unmarried</td>
<td>7(15.9)</td>
<td>2(6.1)</td>
<td>9(11.7)</td>
</tr>
<tr>
<td></td>
<td>Married</td>
<td>37(84.1)</td>
<td>23(69.7)</td>
<td>60(77.9)</td>
</tr>
<tr>
<td></td>
<td>Widowed</td>
<td>0(0.0)</td>
<td>8(24.2)</td>
<td>8(10.4)</td>
</tr>
<tr>
<td>Education</td>
<td>Illiterate</td>
<td>5(11.4)</td>
<td>7(21.2)</td>
<td>12(15.6)</td>
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<tr>
<td></td>
<td>Primary</td>
<td>31(70.5)</td>
<td>23(69.7)</td>
<td>54(70.1)</td>
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<td></td>
<td>Middle</td>
<td>6(13.6)</td>
<td>2(6.1)</td>
<td>8(10.4)</td>
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<td></td>
<td>Secondary +</td>
<td>2(4.5)</td>
<td>1(3.0)</td>
<td>3(3.9)</td>
</tr>
<tr>
<td>Occupation</td>
<td>Daily wagers</td>
<td>10(22.7)</td>
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<td>10(13.0)</td>
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<tr>
<td></td>
<td>Homemakers</td>
<td>0(0.0)</td>
<td>27(81.8)</td>
<td>27(35.1)</td>
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<tr>
<td></td>
<td>Salaried</td>
<td>8(18.2)</td>
<td>2(6.1)</td>
<td>10(13.0)</td>
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<td>Business</td>
<td>5(11.4)</td>
<td>0(0.0)</td>
<td>5(6.5)</td>
</tr>
<tr>
<td></td>
<td>Retired</td>
<td>2(4.5)</td>
<td>1(3.0)</td>
<td>3(3.9)</td>
</tr>
<tr>
<td></td>
<td>Students</td>
<td>3(6.8)</td>
<td>2(6.1)</td>
<td>5(6.5)</td>
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<tr>
<td></td>
<td>Others</td>
<td>16(36.4)</td>
<td>2(6.1)</td>
<td>18(23.4)</td>
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<td>1(3.0)</td>
<td>9(11.7)</td>
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<td></td>
<td>TB Unit</td>
<td>22(50.0)</td>
<td>7(21.2)</td>
<td>29(37.7)</td>
</tr>
<tr>
<td></td>
<td>STI Clinic</td>
<td>2(4.5)</td>
<td>1(3.0)</td>
<td>3(3.9)</td>
</tr>
<tr>
<td></td>
<td>Antenatal Clinic</td>
<td>0(0.0)</td>
<td>8(24.2)</td>
<td>8(10.4)</td>
</tr>
<tr>
<td></td>
<td>NGO</td>
<td>3(6.8)</td>
<td>0(0.0)</td>
<td>3(3.9)</td>
</tr>
<tr>
<td>Route of Transmission</td>
<td>Heterosexual</td>
<td>39(88.6)</td>
<td>31(93.9)</td>
<td>70(90.9)</td>
</tr>
<tr>
<td></td>
<td>Homosexual</td>
<td>2(4.5)</td>
<td>0(0.0)</td>
<td>2(2.6)</td>
</tr>
<tr>
<td></td>
<td>Blood Transfusion</td>
<td>1(2.3)</td>
<td>1(3.0)</td>
<td>1(1.3)</td>
</tr>
<tr>
<td></td>
<td>Infected Needles/ others</td>
<td>2(4.5)</td>
<td>2(6.1)</td>
<td>4(5.2)</td>
</tr>
</tbody>
</table>

Nearly 70% of HIV+ males as well as females had only primary schooling. 11% males and 21% females were illiterate. 23% of males were daily wage labourers, 18% were salaried and 11% had their own business. Majority of females (82%) were homemakers and only 6% were salaried (Table 1).

Nearly 38% of the subjects were referred from tuberculosis unit running under Revised National Tuberculosis Control Programme (RNTCP), 12% from government health facility, 10% from antenatal clinic, 5% from STI clinic and 3% from Non-governmental organizations (NGOs) and 32% were self reported. In majority of the patients possible route of transmission was heterosexual (90%), 5.2% from infected needles, 2.6% homosexual and 1.3% from blood transfusion during treatment in health care facilities. Mean CD4 count at the time of diagnosis was 190.48 ± 180.52 in males and 286.21 ± 220.25 in females (Table 2 & 3).

It was observed that 54.5% of males and 30.3% of females had co-infection with tuberculosis. Odds of HIV-TB co-infection was higher among male as compared to females ($x^2=4.49$, p=0.034, odds ratio= 2.76 (1.07-7.14)). Mean CD4 count among PLWHA co-infected with tuberculosis was 152.03, which was significantly lower than mean CD4 count (297.74) of those without co-infection (t= 3.34, p=0.0013). Sex-wise analysis revealed significant difference only in males (t=2.26; p=0.029) and not in females (t=1.94; p=0.06).

**DISCUSSION**

The mean age of PLWHA in our study was 31.18 ± 8.85 years in males and 30.30 ± 10.07 years in females. This is consistent with the findings of other studies. However, this is in contrast to a study done in Thailand, which revealed that women aged less than 16 years had a higher prevalence. In our study 57% of HIV positive individuals were males which is lower than finding of other studies where 62.51% of HIV positive individuals were males. Males had 1.6 times more chance of being positive as compared to females (CI 1.321-2.022). In our study the infection in men was highest among daily wagers labourers (23%), salaried (18%) and those having own business (11%). Majority of females 82% were housewives and only 6% were salaried. Similar findings were noted in several studies. Majority
of clients were daily wage workers in the low socio economic background (34.94%) followed by housewives (31.72%), salaried individuals (12.23%) and students (11.08%). Majority of HIV positive clients were daily wage workers in the low socio economic background (52.18%). This result was in contrast with the finding of other studies where the incidence of HIV infection was highest among the unemployed youth (49%) and business personnel (35%). In other studies in India it was highest among the manual laborers, followed by truck drivers.

HIV is a preventable disease and improved awareness and changes in behavior practices can bring down the transmission. Socioeconomic status measured by individual’s income, occupation, or education reflects their position in the society and is one of the key predictors of sickness and health. People with lower socioeconomic status are more likely to contract and transmit HIV/AIDS, perhaps because they have inadequate knowledge about the modes of transmission of HIV and preventive measures. They are more likely to use drugs and practice unsafe sex to escape from stress.

Increased awareness and knowledge about the disease is very essential to protect self from the disease by using appropriate precautions. School education has been known to play a significant role in preventing early sexual initiation and risky sexual behavior. People with lower socioeconomic status are more likely to contract and transmit HIV/AIDS, perhaps because they have inadequate knowledge about the modes of transmission of HIV and preventive measures. They are more likely to use drugs and practice unsafe sex to escape from stress.

In our study, most common possible route of transmission was heterosexual (90%), 5.2% from infected needles, 2.6% homosexual and 1.3% from blood transfusion during treatment in health care facilities. These results are similar with the findings of other studies. In one of the study done by Devi BS IDU was the most common risk factor (87%) and it was most commonly found among the unemployed youths sharing the needless. Persons with high risk of HIV and spouses of affected individuals need to be educated regarding all levels of prevention of HIV. Patients who are already HIV positive should be counseled about the importance of antiretroviral treatment that it not only prolongs the life but is also effective in reducing the transmission of the disease and decreasing the overall viral load. Best antidote to the HIV/AIDS challenge remains increased awareness and adoption of safe behavioural practices and the solution lies in planning and designing the IEC activities keeping in mind the specific situations in the area.

National AIDS control organization (NACO) also has reported TB as the commonest opportunistic infection (62.3%) in the HIV infected persons. In this study, 54.5% of males and 30.3% of females had co-infection with tuberculosis, with higher risk in males. This is consistent with the findings in another study but contrasting results were found in other studies. 5.06% had co-infection with T.B. In our study Mean CD4 count among patients co-infected with tuberculosis was significantly lower. This is similar to the results of study done in Ethiopia where the mean CD4 + lymphocyte count of HIV mono-infected participants were 296 ± 192 Cells/mm3 and tuberculosis-HIV co-infected patients had lower mean CD4+ lymphocyte count of 199 ± 149 Cells/

### Table 3. CD4 Count of HIV positive persons and co-infection with TB

<table>
<thead>
<tr>
<th>CD4 Count</th>
<th>Males (n=44)</th>
<th>Female (n=33)</th>
<th>All Subjects (N=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200</td>
<td>3</td>
<td>15.0</td>
<td>12</td>
</tr>
<tr>
<td>200-399</td>
<td>6</td>
<td>30.0</td>
<td>6</td>
</tr>
<tr>
<td>400+</td>
<td>6</td>
<td>30.0</td>
<td>1</td>
</tr>
<tr>
<td>Missing</td>
<td>5</td>
<td>25.0</td>
<td>5</td>
</tr>
<tr>
<td>Mean</td>
<td>254.9±216.5</td>
<td>136.8±124.8</td>
<td>336.7±235.8</td>
</tr>
<tr>
<td>Test of Significance</td>
<td>t=2.26; p=0.029 (Significant)</td>
<td>t=1.94; p=0.06 (Not significant)</td>
<td>t=3.34; p=0.0013 (Significant)</td>
</tr>
</tbody>
</table>
mm3 with p value = 0.007. Lower CD4+ lymphocyte count was found to be the only predicting factor for co-infection. Early detection of co-infection is very necessary to prolong their ART initiation time and thereby strengthening their immune status. In this study, nearly 38% of the subjects were referred from tuberculosis unit running under revised national tuberculosis programme (RNTCP), 32% were self reported and 30% from other healthcare facilities. This finding is important to set up a cross-referral network between various units functioning in the hospital and other service providers in the area. In another study done by Ingole N, majority of individuals were direct walk-in clients who were referred by clinicians (provider initiated testing).  

The changing face of the HIV/AIDS epidemic and dual burden of HIV-TB co-infection warrants improved access to voluntary HIV counseling and testing. As access to HIV treatment becomes more widely available, the need for identification and linking of positive patients to care and support services would become even greater. Under National TB/HIV framework, a new model has started which requires all TB patients under RNTCP service providers referred to Integrated Counseling and Testing Centers (ICTCs) and “TB-suspects” are referred from ICTC to RNTCP facilities for diagnosis and treatment of TB. HIV–TB co-infected patients are then referred to Anti Retroviral Treatment (ART) center for initiation of ART between two weeks and two months of initiating TB treatment. Although, significant efforts are being made at the national level, it is essential to make efforts at the micro level to achieve system of cross-referrals with sustainable results. Also, the data generated at each center should be analyzed regularly to understand the demographic profile and use the generated knowledge towards enhanced management of the dual epidemic.

Acknowledgement

We acknowledge the efforts of the Medical officer, counselor and laboratory technician of ICTC of PHC Palam.

REFERENCES

5. Devi SB; Naorem S; Singh TJ; Singh KB; Prasad L. HIV and TB Co-infection. JIAGM 2005;6(3):220-3
A SIMPLE AND RAPID LIQUID CHROMATOGRAPHY METHOD FOR DETERMINATION OF LEVOFLOXACIN IN PLASMA

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ABSTRACT

Introduction: Levofloxacin (LFX) is one of the second line anti-tuberculosis drugs used in the treatment of multi drug resistant tuberculosis. Monitoring of LFX concentrations in plasma may be valuable to study its pharmacokinetics and drug-drug interaction when co-administered with other anti-tuberculosis drugs. We developed a high performance liquid chromatographic method of determination of LFX in plasma.

Methodology: The method involved deproteinisation of the sample with perchloric acid and analysis of the supernatant using a reversed-phase C18 column (150mm) and fluorescence detection at an excitation wavelength of 290 nm and an emission wavelength of 460 nm.

Results: The assay was specific for LFX and linear from 0.25 to 10.0µg/ml. The relative standard deviation of intra- and inter-day assays was lower than 10%. The average recovery of LFX from plasma was 99%.

Conclusion: A sensitive, specific and validated method for quantitative determination of LFX in plasma was developed. Due to its simplicity, the assay can be used for pharmacokinetic studies of LFX.

Key words: Levofloxacin, Plasma, HPLC, Fluoroquinolones

INTRODUCTION

Tuberculosis remains one of the main causes of mortality and morbidity worldwide. The emergence of multi-drug resistant strains of M. tuberculosis strains in some parts of the world has become a major concern. The anti-tuberculosis activity of the fluoroquinolones has been under investigation since the 1980s.1 Levofloxacin (LFX) represents one of the few second-line drugs introduced in the therapeutic regimens for Multi-drug resistant tuberculosis.2 Studies have shown that LFX has higher in vitro activity compared to older fluoroquinolones and was well-tolerated and safe in multi-drug resistant tuberculosis patients.2

Both levofloxacin and moxifloxacin were shown to possess equivalent efficacy for treating multi-drug resistant tuberculosis.3 Monitoring of LFX concentrations in plasma may be valuable to study its pharmacokinetics and drug-drug interactions when co-administered with other anti-tuberculosis drugs.

Several high performance liquid chromatography methods using both fluorescence and ultraviolet detectors have been developed for measuring plasma LFX concentrations.4-16 While few methods are simple, some of the methods are quite cumbersome and time consuming. These methods have not checked for interference of anti-tuberculosis drugs in their specificity experiment. Since LFX is used alone with anti-tuberculosis drugs, it is essential to rule out interference of these drugs in the assay of levofloxacin. We developed and validated a simple and rapid assay procedure for estimation of LFX in plasma based on the method that we had earlier developed for ofloxacin and moxifloxacin.17,18
METHODOLOGY

Pure LFX powder was purchased from Sigma Aldrich Chemical Company, MO, USA, moxifloxacin from Selleck Chemicals LLC, USA, acetonitrile (HPLC grade) from Merck (India), potassium dihydrogen orthophosphate and perchloric acid from Qualigens (India) were used. Deionized water was processed through a Milli-Q water purification system (Millipore, USA). Pooled human plasma was obtained from Lions Blood Bank, Chennai, India.

Chromatographic System

The HPLC system (Shimadzu Corporation, Kyoto, Japan) consisted of two pumps (LC-10ATvp), fluorescence detector (RF-10AXL) and auto sampler (SIL-HTA) with built in system controller. Class VP-LC workstation was used for data collection and acquisition. The analytical column was a C18, 150 mm x 4.6 mm ID, 5 um particle size (Lichrospher 100 RP-18e, Merck, Germany) protected by a compatible guard column.

The mobile phase consisted of 0.05 M phosphate buffer, pH 2.6 (adjusted with 1 N hydrochloric acid) and acetonitrile (80:20, v/v). Prior to preparation of the mobile phase, the phosphate buffer and acetonitrile were degassed separately using a Millipore vacuum pump. The fluorescence detector was set at an excitation wavelength of 290 nm and an emission wavelength of 460 nm. The chromatogram was run for 7 minutes at a flow rate of 1.2 ml/min at ambient temperature. Unknown concentrations were derived from linear regression analysis of the peak height ratios (analyte/internal standard) vs. concentration curve. The linearity was verified using estimates of correlation coefficient (r).

Preparation of standard solution

A stock standard (1 mg/ml) was prepared by dissolving LFX in 0.1N hydrochloric acid. The working standards of LFX in concentrations ranging from 0.25 to 10.0 µg/ml were prepared in pooled plasma.

Sample preparation

To 50 µl each of calibration standards and test samples (from healthy volunteers), 10 µl of moxifloxacin (internal standard) was added at a concentration of 100µg/ml. This was mixed with 25µl of 7% perchloric acid, the contents were vortexed vigorously, and centrifuged at 10,000 rpm for 10 min. 20 µl of the clear supernatant was directly injected to the HPLC column.

Accuracy and Linearity

The accuracy and linearity of LFX standards were evaluated by analysing a set of standards ranging from 0.25 to 10.0µg/ml. The within day and between day variations were determined by processing each standard concentration in duplicate for six consecutive days.

Precision

In order to evaluate the precision of the method, three different plasma samples from healthy subjects containing varying concentrations of LFX were analysed in duplicate on three consecutive days.

Recovery

For the recovery experiment, known concentrations of LFX (0.25, 0.5, 2.5, 5.0& 10.0 µg/ml) were prepared in pooled human plasma samples and were spiked with 0.5, 1.25 and 2.5 µg/ml LFX and assayed after addition of the internal standard. The percentage of recovery was calculated by dividing sample differences with the added concentrations. Recovery experiments were carried out on three different occasions.

Interference from endogenous compounds was investigated by analysing blank plasma samples obtained from six each of male and female subjects. Interference from certain anti-tuberculosis drugs such as rifampicin, isoniazid, pyrazinamide, ethambutol, streptomycin, ethionamide, cycloserine and certain antiretroviral drugs, namely, nevirapine, efavirenz, zidovudine, didanosine, stavudine, lamivudine, saquinavir, lopinavir, ritonavir and indinavir at a concentration of 10µg/ml was also evaluated.

Limits of quantification (LOQ) and detection (LOD)

These values were estimated mathematically from the standard curve equations. The LOQ was obtained by multiplying the standard deviation (SD) of the Y-axis intercepts by 10. The LOD was equal to 3.3 times the SD of the Y-axis intercepts 19.
Samples

The method developed and validated was applied in plasma samples obtained from multi drug resistant tuberculosis patients who receive LFX as part of their anti-tuberculosis treatment. Blood samples were collected from these patients, who were admitted in the Government Hospital of Thoracic Medicine, Tambaran, Chennai for the pharmacokinetic study. Their age and body weight ranged from 35 to 60 years and 48 to 70 kg respectively. These patients are administered with 1000 mg LFX along with other second line anti-tuberculosis drugs. Two milliliters of blood was collected at two hours after directly observed drug administration in a heparinised vacutainer tube. Plasma was separated and stored at -20°C. Estimation of plasma LFX was undertaken within 48 hours of blood collection. The study commenced after obtaining approval from the Institutional Ethics Committee. Informed, written consent was obtained from the study patients before they took part in the study.

RESULTS AND DISCUSSION

In this study, sample preparation required a simple one-step deproteinisation method and analysis using a C18 column and an isocratic mobile phase. The present method has the advantages of being rapid (run time is only 7 minutes) and using a small sample volume (50 microlitres), without any loss of analyte. The use of internal standard helped in monitoring the recovery of LFX from plasma. Moxifloxacin was chosen as the internal standard since the present method was a modification of an earlier method that we had developed for estimation of moxifloxacin in plasma and urine, and it had a different retention time to that of LFX.

Under the chromatographic conditions described above, LFX was well separated as seen in the representative chromatograms (Figure 1a, b). The retention times of LFX and internal standard were 1.9 and 4.5 minutes respectively. Blank plasma samples did not give any peak at the retention times of LFX and moxifloxacin (Figure 1c). The lowest concentration of LFX gave a discrete peak at 4.5 minutes (Figure 1a). A representative chromatogram of a healthy volunteer’s plasma sample following extraction and analysis is shown in Figure 1d.
In view of its potent anti-mycobacterial activity, LFX is used in the treatment of tuberculosis along with first and second line anti-tuberculosis drugs. It, therefore, becomes necessary to rule out interference of anti-tuberculosis drugs in the assay of LFX and establish the specificity of the method. No endogenous substances or anti-tuberculosis drugs such as rifampicin, isoniazid, pyrazinamide, ethambutol, streptomycin, ethionamide, cycloserine or antiretroviral drugs such as nevirapine, efavirenz, zidovudine, didanosine, stavudine, lamivudine, saquinavir, lopinavir, ritonavir and indinavir interfered with the LFX chromatogram.

The minimal inhibitory concentration (MIC) of LFX against *M. tuberculosis* is 0.5µg/ml. After a daily oral dose of 1000 mg LFX, the mean maximum plasma concentration of LFX at steady state is 8.24 µg/ml; this is attained at 2 hours post-dosing. In the present method, LFX concentrations ranging from 0.25-10.0µg/ml were checked for linearity. These concentrations span the range of clinical interest, the lowest concentration of 0.25µg/ml being lower than the MIC of the drug. The calibration curve parameters of levofloxacin from six individual experiments for standard concentrations ranging from 0.25 to 10.0µg/ml showed a linear relationship between peak height ratio and concentrations (Figure 2).

The % variations from the actual ranged from 96 to 106%. The LOD and LOQ estimated mathematically from the standard curve equation were 0.04µg/ml and 0.12µg/ml respectively. The method reliably eliminated interfering material from plasma, yielding a recovery for LFX that ranged from 96 to 104%.

The method described was applied for the determination of LFX concentration in plasma from 10 healthy subjects who received a single oral dose of 500mg LFX. A mean plasma peak concentration of 5.61µg/ml was obtained at two hours, the range being 3.21 to 8.03µg/ml. This value is similar to that reported by Tsaganos and others. The assay spans the concentration range of clinical interest.

Several HPLC methods have been described to measure LFX levels in plasma for pharmacokinetic studies. The sample preparation used in the method described by Zhou et al. involves liquid-liquid extraction, evaporating the organic phase to dryness and reconstituting the dried residue in
the mobile phase. This could be time consuming compared to the one-step sample preparation procedure that we describe here. Siewert has used a gradient mobile phase, which could be quite complex compared to an isocratic mobile phase as described in our method.7 Methods using liquid-solid extraction using oasis cartridges have also been reported15; this could be quite expensive. Other methods have used pre-column processing9 or ultrafiltration9 for estimation of plasma LFX.

CONCLUSION

A sensitive, specific and validated method for quantitative determination of LFX in plasma is described. This rapid, accurate and reproducible method utilises a single step extraction. The chromatogram yields a well-resolved peak for LFX with good intra- and inter-day precision. The easy sample preparation and small sample size makes this assay highly suitable for pharmacokinetic studies of LFX in tuberculosis patients.

Acknowledgement

The authors thank all the healthy volunteers who took part in this study and also acknowledge the secretarial assistance rendered by Ms. A. Leelavathi.

REFERENCES


STUDY OF THE CLINICAL CHARACTERISTICS AND OUTCOMES OF EXUDATIVE PLEURAL EFFUSION: IMPROVING CLINICAL DECISION MAKING IN RESOURCE LIMITED SETTING

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ABSTRACT

Introduction: In the background of resource limited setting like Nepal, we set out to identify if specific clinical characteristics and basic lab parameters would guide differentiation of Tuberculous from other causes of exudative pleural effusion.

Methodology: Retrospective study of 109 consecutive patients with exudative pleural effusion.

Results: Compared to Tubercular pleural effusions (41.3%), increased age, increased duration of symptom and increased pack years statistically favoured a diagnosis of Malignant pleural effusion (21.1%), whereas presence of fever, cough and increased pleural ADA levels favoured Tubercular pleural effusions. With regards to Parapneumonic effusions (26.6%), a shorter duration of symptom, smaller effusions, higher pleural Neutrophils, lower pleural lymphocyte neutrophil ratio and lower ADA favoured the diagnosis as compared to Tubercular pleural effusions.

Conclusions: The appreciation of important clinical and pleural biochemical differences between Tubercular and other major causes of exudative pleural effusions aids in improved clinical decision making with minimal resources in resource limited settings like ours.

Key words: Exudative Pleural Effusion, Tuberculosis, Clinical Decision Making

INTRODUCTION

Pleural effusion is a common presentation in the patients presenting to the Pulmonologists. The etiology of Pleural Effusion depends on geographic region, patient characteristics, and the availability of diagnostic facilities in that region. Pleural effusions can be transudative or exudative.¹,² In cases with transudative pleural effusion the diagnosis is usually made without much difficulties but exudative pleural effusion requires careful differential diagnosis that includes parapneumonic effusion, tuberculosis, and metastatic cancers which are found to be the cases in large number of patients.³⁵ Tuberculosis is the most common cause of exudative pleural effusion in many areas of the world.⁶⁷ In Nepal, Tuberculosis (TB) is a major public health problem. About 45 percent of the total population is infected with TB, of which 60 percent are adult. Every year, 45,000 people develop active TB, out of them 20,580 have infectious pulmonary disease. These 20,000 are able to spread the disease to others.⁸ Although pulmonary disease is the most common form of TB, extra-pulmonary TB affecting mainly the lymph nodes and pleura serves as the initial presentation in about 25% of adults. Pleural TB accounts for 4% of all TB cases in the United States; in Spain, however, this percentage is greater than 10%.¹⁰ TB is one of the most common causes of pleural effusion in some geographical areas.¹¹ But in the developed world like United States, the leading etiologies of pleural effusion in adults who undergo thoracentesis are CHF, pneumonia, malignancy, pulmonary embolus, viral disease, coronary artery bypass surgery, and cirrhosis with ascites.¹² Thus it

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becomes very important to understand the clinical characteristics of the causes of Pleural effusion as the treatment, social and economic implications of the diagnosis being Tuberculous or Non- Tuberculous are tremendous.

**METHODOLOGY**

We conducted a retrospective review of the medical records and chest radiographs of consecutive cases of exudative pleural effusions referred to the Respiratory and Internal Medicine services of the B P Koirala Institute of Health Sciences, Nepal during a 15 month period from April 2013 till July 2014. The hospital serves as a referral hospital for the whole of Eastern Nepal. Effusions were classified as exudates when they satisfied Light’s criteria or if frank pus was present.

In the cases with exudative pleural effusion, the relevant data were scanned and included in the study only if the patient chart was viewed as Complete. Complete chart was defined as having detailed epidemiological data, a complete medical history and clinical examination, investigations including Pleural fluid analysis for TC/DC/sugar/protein/light’s criteria, ADA and malignant cytology if diagnosis was inconclusive by routine analysis, other special tests of pleural fluid as required, like, Amylase etc. Only the initial fluid examination was recorded. Once the above parameters were present, the Digital Radiographic Library was explored. The X-Ray was reviewed by a Pulmonology trainee. The size of the effusion was estimated on the initial upright inspiratory posteroanterior chest film. Effusions were classified as; large effusion if effusion covered greater than 50 percent of the hemithorax, medium if 25 to 50 percent was covered, and small effusion if effusion covered less than 25 percent of the hemithorax. The patient’s with the following features were classified as Tuberculous pleural effusion.

1. Positive mycobacterial culture in pleural fluid or pleural biopsy tissue samples.
2. Granulomatous inflammation in pleural biopsy tissue samples.
3. Positive AFB stain or mycobacterial culture of sputum sample.
4. Clinically suspected tuberculous pleurisy and pleural effusion that were resolved with anti-TB treatment. Here, ‘clinical suspicion’ means that these patients had no systemic diseases, and were excluded from malignancy and other pleural diseases. Moreover, there were suggestive clues of TB from contact history, radiographical findings or clinical presentation.
5. ADA level of more than 60 with response to anti-TB treatment during hospital stay will also be taken as TB.

All other cases of exudative pleural effusion with complete medical charts were classified as Non-Tuberculous effusion. These were diagnosed in accordance to the following criteria:

**Parapneumonic effusion:** Pleural effusion in association with pneumonia, lung abscess, or bronchiectasis.

**Empyema:** Presence of purulent fluid or positive culture of parapneumonic effusion.

**Neoplasia:** Neoplastic tissue in the pleural cavity (biopsy and/or cytology) or CT suspicion of malignancy if biopsy and cytology were inaccessible or inconclusive.

Other diagnosis made such as, cirrhosis of the liver, pancreatitis, systemic lupus erythematosus, rheumatoid arthritis, were as per the pre-established criteria.

**Statistical analysis**

Data with parametric distribution have been expressed in mean ± SD and Independent t-test was used for the comparison of variables. Data with non parametric distribution have been expressed as median (25th percentile and 75th percentile) and Mann Whitney test was used for the comparison of variables. The chi-squared analysis was used for comparison of proportions. All statistical test values were two-sided, and a P value of <0.05 was considered to be statistically significant. Analysis was carried out using SPSS 17 software.

**RESULTS**

Among 109 patients, 58.7% (64) of the patients were male and the mean age was 47.97(±19.69) years. The mean age in patients with Tuberculous pleural effusion (TPE) was 42.3(±18.9) years and that in Malignant pleural effusion (MPE) was 65.5(±13.6) years. The etiological distribution of the pleural effusions with the number of patients in each etiological group and the mean age of the group are shown in Table 1. 41.3%(45) of the cases were Tuberculous in origin and there was 1
A case of Hepatitis A associated pleural effusion. The majority of parapneumonic effusions (82.4%) were small in size whereas 39.1% of MPE were large; the majority of TPE were Medium in size (57.8%). Table 1. Causes, gender and age at diagnosis of pleural effusion

<table>
<thead>
<tr>
<th>Causes</th>
<th>n</th>
<th>%</th>
<th>Males/Females</th>
<th>Age, yrs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubercular Pleural Effusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>45</td>
<td>41.3</td>
<td>27/18</td>
<td>42.3±18.9</td>
</tr>
<tr>
<td>Non Tubercular Effusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant Pleural Effusion</td>
<td>23</td>
<td>21.1</td>
<td>12/11</td>
<td>65.5±13.6</td>
</tr>
<tr>
<td>U&amp;C</td>
<td>17</td>
<td>15.6</td>
<td>9/8</td>
<td>44.1±17.7</td>
</tr>
<tr>
<td>Parapneumonic Effusion</td>
<td>12</td>
<td>11.0</td>
<td>11/1</td>
<td>40.25±17.0</td>
</tr>
<tr>
<td>Empyema</td>
<td>5</td>
<td>4.5</td>
<td>3/2</td>
<td>53±20.7</td>
</tr>
<tr>
<td>Hydropneumothorax</td>
<td>1</td>
<td>0.9</td>
<td>0/1</td>
<td>81±10</td>
</tr>
<tr>
<td>RA</td>
<td>2</td>
<td>1.8</td>
<td>1/1</td>
<td>41±2.8</td>
</tr>
<tr>
<td>Metastatic Pleural Effusion</td>
<td>3</td>
<td>2.8</td>
<td>0/3</td>
<td>48±6.2</td>
</tr>
<tr>
<td>Others#</td>
<td>1</td>
<td>0.9</td>
<td>1/0</td>
<td>16±1.0</td>
</tr>
</tbody>
</table>

*Mean ± SD, # Hepatitis A associated pleural effusion

The diagnosis of TB was on the basis of high ADA in 68.9% of the cases (Table 2). The ADA was less than 60 in 10 of TPE and in 4 cases ADA were not done. Comparatively, ADA of more than 60 was present in 5(21.7%) of MPE cases and in 5 (41.7%) of the cases with Empyema.

On comparing the clinical and demographic characteristics, the subset of patients with MPE compared to TPE (Table 3) had a greater mean age (65±13 years vs 42±18 years), longer duration of symptoms (median duration 60 days vs 30 days), and they had a longer Smoking history in terms of the Pack years (median duration 30 years to 5 years). The subset with TPE had fever predominantly whereas chest pain was more common in the MPE subset.

On comparing the subset of patients with Parapneumonic effusion (PPE) to TPE (Table 3), the duration of symptom was longer in the Tuberculous group (median duration 8 days to 30 days) whereas the duration of hospitalization (median duration 10 days to 6 days) was longer in the PPE subset, also the size of the effusions where Small in this group compared to the TPE group.
On comparing the subset of patients with PPE to TPE (Table 4), the patients with PPE showed an increased percentage of pleural neutrophils (median value 85% vs 30%), a decreased percentage of pleural lymphocytes and consequently a lower pleural lymphocyte to neutrophil ratio (median value 0.17 vs 2.33). Pleural fluid ADA levels were significantly higher in the Tubercular group of the patients (median value 90U/l to 31U/l). Out of the PPE cases, 12 had empyema and in total 13 patients required thoracostomy.

In the group with TPE, 11 (24.4%) had Large effusions and Steroids had to be added to 9 of these cases.

### Table 4. Comparison of Pleural fluid analysis of patients with tubercular and non-tubercular effusion

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Tubercular pleural effusion (n=45)</th>
<th>Malignant pleural effusion (n=23)</th>
<th>Para-pneumonic effusion (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural fluid TLC per mm³</td>
<td>Median (Interquartile Range)</td>
<td>Median (Interquartile Range)</td>
<td>p</td>
</tr>
<tr>
<td></td>
<td>330 (55-630)</td>
<td>300 (140-800)</td>
<td>.645</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(10-720)</td>
</tr>
<tr>
<td>Pleural neutrophils, %</td>
<td>Median (Interquartile Range)</td>
<td>Median (Interquartile Range)</td>
<td>p</td>
</tr>
<tr>
<td></td>
<td>30 (20-70)</td>
<td>60 (20-80)</td>
<td>.297</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(85)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(67.5-90)</td>
</tr>
<tr>
<td>Pleural lymphocytes, %</td>
<td>Median (Interquartile Range)</td>
<td>Median (Interquartile Range)</td>
<td>p</td>
</tr>
<tr>
<td></td>
<td>70 (30-80)</td>
<td>40 (20-80)</td>
<td>.297</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(10-32.5)</td>
</tr>
<tr>
<td>Pleural lymphocyte to neutrophil ratio</td>
<td>Median (Interquartile Range)</td>
<td>Median (Interquartile Range)</td>
<td>p</td>
</tr>
<tr>
<td></td>
<td>2.33 (4.2-4.00)</td>
<td>.67 (25-2.34)</td>
<td>.096</td>
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<td></td>
<td></td>
<td></td>
<td>(0.71)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(11.1-47)</td>
</tr>
<tr>
<td>Pleural glucose, mg/dL</td>
<td>Median (Interquartile Range)</td>
<td>Median (Interquartile Range)</td>
<td>p</td>
</tr>
<tr>
<td></td>
<td>68 (51.5-151)</td>
<td>86 (54-106)</td>
<td>.693</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(21)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(11.5-115.5)</td>
</tr>
<tr>
<td>P/S protein ratio</td>
<td>Median (Interquartile Range)</td>
<td>Median (Interquartile Range)</td>
<td>p</td>
</tr>
<tr>
<td></td>
<td>.66 (.14)*</td>
<td>.64 (.12)*</td>
<td>.694</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(63)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(.23)</td>
</tr>
<tr>
<td>Pleural Protein more than 5g/dl</td>
<td>Median (Interquartile Range)</td>
<td>Median (Interquartile Range)</td>
<td>p</td>
</tr>
<tr>
<td></td>
<td>17 (37.8%)#</td>
<td>1 (4.3%)#</td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(20.7%)#</td>
</tr>
<tr>
<td>Pleural LDH, U/L</td>
<td>Median (Interquartile Range)</td>
<td>Median (Interquartile Range)</td>
<td>p</td>
</tr>
<tr>
<td></td>
<td>520 (341-693)</td>
<td>506.50 (312-583)</td>
<td>.702</td>
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<td>(420)</td>
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<td></td>
<td></td>
<td></td>
<td>(341-738)</td>
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<tr>
<td>P/S LDH ratio</td>
<td>Median (Interquartile Range)</td>
<td>Median (Interquartile Range)</td>
<td>p</td>
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<tr>
<td></td>
<td>1.03 (.85-1.68)</td>
<td>1.30 (.85-1.84)</td>
<td>.466</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1.26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1.03-1.92)</td>
</tr>
<tr>
<td>Pleural ADA, U/L</td>
<td>Median (Interquartile Range)</td>
<td>Median (Interquartile Range)</td>
<td>p</td>
</tr>
<tr>
<td></td>
<td>80 (61-113)</td>
<td>40 (20-52)</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(31)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(24.5-127)</td>
</tr>
</tbody>
</table>

*Mean ± SD, #total number(percentage of total)

**DISCUSSION**

In a developing country like Nepal, even the tertiary care hospitals have at best ordinary facilities. Though the scenario is gradually changing with Nepal developing its own specialists and thus the scope of investigations and diagnosis gradually increasing day by day, it is still limited by cost factors and lack of Universal health coverage that is the case in the West. In this background, we tried to focus if differences in clinical and basic lab parameters to differentiate TPE from NTPE would improve clinical decision making.

With regards to the cut off level for ADA, Some large series suggest that a value >45 to 60 U/L is 100 percent sensitive and up to 97 percent specific for TPE.\textsuperscript{15-19} Pleural effusions with an ADA level <40 U/L are rarely caused by TB.\textsuperscript{20} Since this study was conducted in a resource limited setting, we wanted to increase the Specificity of the diagnosis of TPE and thus used ADA value of more than 60U/l as cut off.

As expected, TPE was the commonest cause of exudative pleural effusion (41.3%) over all age groups. When looking at patients less than 40 years of age, the percentage of TPE rose to 63% (29/46), a pattern observed in countries with high incidence of TB.\textsuperscript{15,21,22} Fever, cough and shortness of breath were the most common symptoms occurring in 73% of the cases in agreement with other studies.\textsuperscript{23} TPEs are typically unilateral (95%).\textsuperscript{24} In one series of 254 patients with TB pleurisy, the effusions occupied between one-third and two-thirds of the hemithorax in 46%.\textsuperscript{15} In our study as well, TPE was unilateral in 97.8% of the cases and there was no site predilection, and Medium sized effusion were the most common (57.8%). The pleural fluid in TPE was predominantly lymphocytic in 62.2% of the cases and in 66.7% of the cases the pleural lymphocyte neutrophil ratio was more than 0.75. The use of the ratio is particularly important as Burgess et al.\textsuperscript{25} have shown that Specificity is increased when the lymphocyte to neutrophil ratio is greater than 0.75 and the ADA is greater than 50 U/L. Different studies have shown that the pleural fluid protein in TPE is invariably >3.0 g/dL (30 g/L), and >5.0 g/dL (50 g/L) in 50 to 77 percent of cases.\textsuperscript{26,27} In our study, the pleural fluid protein was >5g/dl in 37.8%(17/45) of the cases whereas a level of >3g/dl was present in 88.9%(40/45) of the cases . We relied heavily on pleural fluid ADA for the diagnosis of TPE and it was >60U/l in 68.9%(31/45). The diagnosis was based on clinical suspicion in only 7 of the cases, positive sputum microscopy in 5 of the cases and positive gene xpet on sputum in 2 of the cases.
Malignancy was the second most common cause of exudative pleural effusions in our study and the most frequent cause among patients older than 60 years. Others have also made the same observation.11 There were 23 cases (21.1%) of MPE as a result of Bronchogenic Carcinoma, whereas 3 more cases were a result of Metastatic Pleural Effusion. The differential diagnosis between TPE and MPE is a very important clinical problem. Compared to TPE, these patients were older in age (mean age 65±13 years) and had symptoms for longer duration of time (median duration 60 days). Fever understandably was more common in TPE than MPE, whereas chest pain was more common in the MPE group which could be due to increased number of larger size effusions as well as parietal and chest wall extension of the tumour. History of Smoking was present in 82% of the cases with MPE whereas only 11% of TPE were smokers. The Median pack years for the MPE group was 30 pack years. These clinic-demographic pictures do point to some distinction in the presentation of MPE compared to TPE. Distinction of MPE and TPE is also difficult by pleural fluid analysis. There was no significant difference in the Total Leukocyte count, pleural lymphocyte percentage, pleural glucose levels or the pleural LDH. However, interestingly, though the pleural to serum protein ratio was similar in both the groups, pleural fluid protein was >5g/dl in 17 (37.8%) of the patients with TPE in comparison to 1 (4.3%) of MPE and this difference was significant.

Measurement of adenosine deaminase (ADA) may be helpful with a differential diagnosis of malignant versus tuberculous pleurisy when an exudative effusion is lymphocytic, but initial cytology and smear and culture for tuberculosis are negative.16,17,28 Specificity is increased when the lymphocyte to neutrophil ratio is greater than 0.75 and the ADA is greater than 50 U/L.25 False negatives and positive ADA results do occur, so ADA results need to be considered in the context of other features of the patient’s clinical presentation.

In our study, the ADA values in TPE and MPE were discriminatory. The median ADA in TPE was 90U/l whereas it was 40U/l in the MPE subset. However, 5/23 (21.7%) of the patient with MPE also had values more than 60U/l, interestingly in all 5 of these cases the pleural fluid protein was <5g/dl, which is a very interesting observation and will be interesting to see if it is replicated in our future studies. Pleural fluid lymphocyte neutrophil ratio though higher in the TPE group was not statistically significant, however there was a trend towards a difference as the p-value was .096.

Parapneumonic effusions together with empyema thoracis accounted for 26.6% of all our cases. It is estimated that about 40% of patients with pneumonia develop a concomitant pleural effusion30 although some studies show the incidence of this complication of pneumonia to be less than 20%.31 Compared to TPE, duration of symptoms at presentation was shorter (median duration 8 days in PPE to 30 days in TPE) which is expected as PPE has more acute presentation whereas TPE is acute or sub-acute in onset. However, these patients were hospitalized longer (median duration 10 days to 6 for TPE), and thoracostomy had to be performed in 44% of these cases. The complicated nature, the need to complete antibiotic course and the complications related to thoracostomy might have led to the longer duration of stay. The size of the effusion was large in only 1 case and majority of them were small (65.5%) and medium in size (31%).

There were quite a few discriminating factors in the pleural fluid analysis. The pleural neutrophils were more in the PPE subset and the pleural lymphocytes less, consequently, the pleural lymphocyte neutrophil ratio was 0.17 in the PPE group and 2.33 in the TPE group.

Pleural fluid glucose was lower in the PPE group however the difference was not statistically significant. Pleural ADA was again discriminatory, with median values of 31U/l in the PPE subset compared to 90U/l in the TPE subset.

CONCLUSION

Thus, using the clinical characteristics and basic lab investigations, features such as increased age, increased duration of symptom, lack of fever, positive Smoking history, lower ADA levels and a lower pleural protein of <5g/dl pointed more towards MPE than TPE. Similarly, decreased duration of symptoms, smaller size of effusion, a higher pleural neutrophil percentage, a lower pleural lymphocyte percentage, a lower pleural lymphocyte to neutrophil ratio and a lower ADA were more in favour of PPE than TPE. The appreciation of these characteristic can aid in the differentiation
of Tuberculous from Non-tuberculous causes of exudative pleural effusion and thus improve the clinical decision making in resource limited setting.

REFERENCES


MAJOR DEPRESSION AMONG PREGNANT MOTHERS WITH HIV: CORRELATES AND SUGGESTED INTERVENTIONS

E Thiruvalluvan

ABSTRACT

Introduction: Psychological disturbance particularly depression is common among people living with HIV infection. More so among pregnant mothers due to concerns with regard to safe delivery, transmission of HIV infection to child, worries about the future and so on. Therefore, this study was undertaken to explore and describe the prevalence and correlates of depression in order to plan an appropriate intervention to ensure quality of life to women with HIV and their children.

Methodology: Antenatal mothers with HIV infection who attended Department of Obstetrics and Gynecology, Government Rajaji Hospital, Madurai between December 2007 and September 2008 for parturition were included in the study. Depression was assessed using the center for epidemiology studies depression scale (CES-D). The scale has 20 items, with a 4 point Likert scale scores ranging from 0-3 for each statement.

Results: A total of 53 respondents were included in the study. Median age of the respondents was 25 years. Despite availability of services of Voluntary Counselling and Testing Centre (VCTC) only 34 respondents underwent HIV screening Depression score. One tenth of them have experienced major depression. Sixteen respondents were depressed on knowing their HIV status, 22 respondents were shocked on receiving of positive results while six respondents attempted to commit suicide. Feeling of discrimination (p=0.003) and thought of abortion after knowing the HIV positive status (p=.003) had significant influence in experience of major depression.

Conclusion: Quality of services of counsellors at antenatal clinics need to be improved and encouraged to periodically assess the psychological needs of antenatal / pregnant mothers. Sensitizing women on methods of family planning should begin during pregnancy and in the post natal period. Referral services should be strengthened further for timely intervention.

Key words: HIV Infected Pregnant Mothers, Depression, and Intervention Strategy

INTRODUCTION

Parent-to-child transmission of HIV accounts for 2.14% of the total HIV infection load in India. Estimates in the year 2006 suggested that national adult HIV prevalence was approximately 0.36 per cent, amounting to 2.34 million (ranging between 2 and 3.1 million) people living with HIV and AIDS.1 Whereas, HIV prevalence among antenatal clinic (ANC) population had wide variation between states. HIV prevalence among antenatal women slightly increased from 1.25% in 2003 to 1.26% in the year 2006 in the state of Andhra Pradesh (AP); while in Tamilnadu the prevalence rate came down from 0.50% to 0.25% during the same period.2

From the psycho social perspective people living with HIV infection particularly women, face a multitude of problems, particularly depression is very common among people living with HIV infection.3,4 Commonly observed psycho social problems ranged from self inhibition to social discrimination. Self inhibition is closely associated with fear of death and perceived social stigma rather than enacted stigma. Psychological disturbances arising out of fear of death, has serious repercussion on the quality of life of people living with HIV. Antenatal mothers found
to be infected with HIV are particularly vulnerable as they face the twin challenge of self and the unknown status of their children to be born. In spite of HIV infection decision to give birth is influenced by particularly social pressure in many societies. Irrespective of the choice, whether personal choice or forced, mere presence of HIV infection itself is likely to generate anxiety in a woman. Anxiety could be with regard to safe delivery, transmission of HIV infection to child, worries about the future and so on. Disclosure of HIV status continues to be a major barrier for emotional well being to an HIV positive individual. Studies reported that perceived stress was associated with disclosure and access and availability of social support on disclosure.

Poorer family cohesion was also observed owing to elevated depression that results in poorer family sociability. Depression also was associated with the mothers being less able to perform routine tasks that they typically do; hence children of more depressed mothers had increased responsibilities for household tasks. According to Murphy et al, 51% of the mothers with HIV infection met DSM-IV diagnostic criteria for a psychological disorder in the preceding year. Posttraumatic stress disorder and major depression are the most commonly diagnosed psychological disorders among women with HIV infection.

High depression scores were associated with women who were no longer in a relationship with their partner, whose babies were HIV-infected, who had not disclosed their HIV status to others and who reported that their HIV-infection was something about which their family would be ashamed of. Hence, it is important to remember that in spite of added social support and medical treatments, HIV-positive women tend to show higher levels of health care discrimination, personal isolation, and psychological sequel than their sero-negative counterparts. Hence, an assessment of presence of major depression in HIV infected mothers was needed to get a clear picture of the prevalence and correlates of depression in order to plan and initiate appropriate intervention to ensure better quality of life to both women and their children.

The present study made an attempt to assess the prevalence of major depression experienced by antenatal HIV positive women in Madurai South India where HIV disproportionately affects the poor and disadvantaged, adding to the burden on the affected people as well as the health care system.

### METHODOLOGY

#### Setting:
The study was carried out in Government Rajaji Hospital, Madurai. Fifty three HIV infected women who delivered a baby between December 2007 and September 2008, were included in the study. Informed consent was obtained prior to administering the interview schedule. The study was approved by the Institutional Ethics Committee and was part of a larger study following HIV infected women and their infants up to 24 months.

#### Data collection:
A semi structured interview schedule was developed for data collection. The interview schedule contained details on socio economic profile, history of health seeking, HIV screening, disclosure and reactions to knowing their HIV status and that of their children, whether drugs to prevent HIV transmission had been taken, feeding choices and reasons for the feeding choice .

Depression was assessed using the CES-D scale. The centre for epidemiology studies depression scale is a widely used 20 item scale that examines the severity of depression. This 4 point Likert scale has scores ranging from 0-3 for each statement. Depression rating is based on the scores as follow:

1. score 22 or more - Major depression
2. Score 15-21- Mild to moderate depression
3. Score less than 15 - No depression.

The scale has been used in India, validated with internal consistency.

#### Data analysis:
The data was entered in and analyzed using SPSS-11 statistical software, frequency tables, cross tabulations were prepared after data coding and cleaning. Levene’s Independent sample test was performed to observe the association between various independent variables and experience of major depression.

### RESULTS

A total of 53 respondents were included in the study. Socio-demographic details such as age, education, occupation, income, husband’s education etc., are given in Table 1. Median age of the respondents
was 25 years. Half of the respondents were above the age of 25 years. Minimum age of the respondents was 20 and the maximum of 35 years. Median age of the spouses was 30 years with the range between 25 years and 46 years.

Two third of the respondents were illiterate. Less than one tenth of respondents had secondary level education. Similarly, one third of spouses were illiterate. Close to 90% of the respondents were daily wage earners and remaining were housewives. Half of the respondents had monthly income of less than US $ 30. Mean family income was INR 2248.98 (SD 1862.4) with the range of INR 500-10000. Forty one percent reported it was their first delivery after seropositivity. Close to half of the respondents came for 2nd delivery. One tenth respondents reported for 3rd or successive deliveries.

Table 1. Socio demographic profile of the study participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sub-variables</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(years)</td>
<td>&lt; 25 years</td>
<td>27</td>
<td>50.9%</td>
</tr>
<tr>
<td></td>
<td>25 or more</td>
<td>26</td>
<td>49.1%</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>53</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Median age</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Standard deviation</td>
<td>3.114</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>Illiterate</td>
<td>17</td>
<td>32.1%</td>
</tr>
<tr>
<td></td>
<td>Primary ed</td>
<td>9</td>
<td>17.0%</td>
</tr>
<tr>
<td></td>
<td>Middle school</td>
<td>17</td>
<td>32.1%</td>
</tr>
<tr>
<td></td>
<td>Secondary &amp; above</td>
<td>10</td>
<td>18.9%</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>53</td>
<td>100.0%</td>
</tr>
<tr>
<td>Occupation</td>
<td>Daily wage</td>
<td>45</td>
<td>84.9%</td>
</tr>
<tr>
<td></td>
<td>House wife</td>
<td>8</td>
<td>15.1%</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>53</td>
<td>100.0%</td>
</tr>
<tr>
<td>Income</td>
<td>Less than 1500</td>
<td>31</td>
<td>58.5%</td>
</tr>
<tr>
<td></td>
<td>More than 1500</td>
<td>22</td>
<td>41.5%</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>53</td>
<td>100.0%</td>
</tr>
<tr>
<td>Order of birth</td>
<td>First child</td>
<td>21</td>
<td>41.2%</td>
</tr>
<tr>
<td></td>
<td>Second child</td>
<td>24</td>
<td>47.1%</td>
</tr>
<tr>
<td></td>
<td>Third or more</td>
<td>8</td>
<td>11.8%</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>53</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

HIV profile:
Details pertaining to HIV screening, such as reason for HIV screening, reactions to HIV positive results, history of HIV in the family screening etc, (Table - 2 ) were available only for 52. Voluntary Counseling and Testing Centre (VCTC) services are made available at the public hospitals across the state of Tamilnadu, India and all pregnant women are encouraged to undergo HIV screening during pregnancy. In spite of this just one third of

Table 2. HIV screening profile of the study participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sub-variables</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reason for HIV Screening</td>
<td>During pregnancy</td>
<td>34</td>
<td>64.15</td>
</tr>
<tr>
<td></td>
<td>After Delivery</td>
<td>3</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td>Owing to husband's status</td>
<td>6</td>
<td>11.3</td>
</tr>
<tr>
<td></td>
<td>Self sickness</td>
<td>4</td>
<td>7.54</td>
</tr>
<tr>
<td></td>
<td>Owing to child's ill health</td>
<td>5</td>
<td>9.43</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>1</td>
<td>1.89</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>53</td>
<td>100.0%</td>
</tr>
<tr>
<td>HIV Status Disclosed by</td>
<td>Counselor</td>
<td>36</td>
<td>67.92</td>
</tr>
<tr>
<td></td>
<td>Doctor</td>
<td>12</td>
<td>22.64</td>
</tr>
<tr>
<td></td>
<td>NGO/Nurses/Hospital workers</td>
<td>4</td>
<td>7.55</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>1</td>
<td>1.89</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>53</td>
<td>100.0%</td>
</tr>
<tr>
<td>Reaction to HIV Status</td>
<td>None</td>
<td>6</td>
<td>11.32</td>
</tr>
<tr>
<td></td>
<td>Suicide attempt</td>
<td>6</td>
<td>11.32</td>
</tr>
<tr>
<td></td>
<td>Shocked</td>
<td>18</td>
<td>33.96</td>
</tr>
<tr>
<td></td>
<td>Depressed</td>
<td>16</td>
<td>30.19</td>
</tr>
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<td></td>
<td>Fear</td>
<td>3</td>
<td>5.66</td>
</tr>
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<td>Could not accept</td>
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<td>1.89</td>
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<td>1.89</td>
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<td></td>
<td>Total</td>
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<td>100</td>
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<tr>
<td>Discriminated Feeling</td>
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<td>7</td>
<td>13.22</td>
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<tr>
<td></td>
<td>No</td>
<td>44</td>
<td>83.02</td>
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<td>2</td>
<td>3.77</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>53</td>
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<tr>
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<td>Less than 2.6 Kg</td>
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</tr>
<tr>
<td></td>
<td>2.6 Kg &amp; above</td>
<td>28</td>
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<td>Premature</td>
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<td>3.77</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>53</td>
<td>100</td>
</tr>
<tr>
<td>ARV to Mother</td>
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<td>37</td>
<td>69.81</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>13</td>
<td>24.52</td>
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<td></td>
<td>Unknown</td>
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<td>5.66</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>50</td>
<td>100</td>
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<tr>
<td>ARV to Newborn</td>
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<td>39</td>
<td>73.58</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>11</td>
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<td>5.66</td>
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<td></td>
<td>Total</td>
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<td>100</td>
</tr>
<tr>
<td>Type of Feeding</td>
<td>Breast feeding</td>
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<td></td>
<td>Bottle feeding</td>
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<td>32.07</td>
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<tr>
<td></td>
<td>Unknown</td>
<td>2</td>
<td>3.77</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>53</td>
<td>100</td>
</tr>
<tr>
<td>Feeding Choice</td>
<td>Money</td>
<td>7</td>
<td>13.20</td>
</tr>
<tr>
<td></td>
<td>Taboo</td>
<td>1</td>
<td>1.88</td>
</tr>
<tr>
<td></td>
<td>On Medical advise</td>
<td>38</td>
<td>71.69</td>
</tr>
<tr>
<td></td>
<td>Emotion</td>
<td>2</td>
<td>3.77</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>2</td>
<td>3.77</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>3</td>
<td>5.66</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>53</td>
<td>100</td>
</tr>
</tbody>
</table>
respondents underwent HIV screening. One tenth of the respondents sought HIV screening only when their children fell sick. One third of respondents were shocked upon receiving their HIV status, while one tenth of respondents attempted to commit suicide. Thirty six percent of respondents were depressed upon knowing their HIV status. Close to one third of respondents reported receiving information from counselors, while one fourth of respondents reported receiving information from doctors. One tenth of respondents felt they were discriminated against because of their HIV status. Due to delay in HIV screening, one fourth of respondents and their children did not receive ARV to prevent mother to child transmission of HIV.

Premature death of the infant was reported by 5.9% of the respondents while 44% had low birth weight infants. Type of feeding practice had an equal mix. Breast feeding was opted by 39% of mothers and bottle feeding was opted by one fourth of mothers. In majority of the respondents (76%), type of feeding was decided basing on medical advice. One tenth of respondents reported money was the reasons for their choice of feeding.

Depression among mothers:

Presence of depression associated with various socio-demographic and clinical aspects is presented in Table 3. Mild to moderate depression was observed in 17.6% of the respondents. Eighty two percent of the respondents were observed to be experiencing major depression. Table 4 respondents aged below 25 years reported higher incidence of depression than their elder counterparts. Respondent who were illiterate or had middle school education (31.4%) reported higher incidence of depression. Daily wage earners were more likely to experience depression due to HIV infection perhaps associated with economic burden. Mothers who reported for 1st and 2nd child birth were more likely to experience major depression. Close to half of the respondents found to be seropositive were delivering the first child. More respondents whose HIV status was disclosed by a counselor reported major depression which highlights the inadequacy in the counseling process. Experience of shock had its impact on the level of depression. Even though fewer respondents reported to have thought of abortion, presence of depression was very high among those who decided to continue with their conception. All those who felt they were discriminated experienced major depression. Respondents who followed their physician’s advice on feeding were emotionally disturbed in some or other way, which resulted in higher incidence of major depression.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sub-variables</th>
<th>Mild to moderate depression</th>
<th>Major depression</th>
<th>Total</th>
<th>Levene’s Test for Equality of Variances</th>
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<td></td>
<td>Count</td>
<td>Count</td>
<td>Count</td>
<td>%</td>
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<tr>
<td>Income</td>
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<tr>
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<td>23</td>
<td>29</td>
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<td>2.986</td>
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<tr>
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<td>22</td>
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<td>53</td>
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<tr>
<td>Thought of Abortion</td>
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<td>4</td>
<td>7</td>
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<td>9.962</td>
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<tr>
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<td>43</td>
<td>81.13</td>
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</tr>
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<td>3</td>
<td>5.66</td>
<td></td>
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<tr>
<td>Total</td>
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<tr>
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<td>3</td>
<td>5.66</td>
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<tr>
<td>Total</td>
<td>8</td>
<td>42</td>
<td>50</td>
<td>100</td>
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### Table 3. Depression in relation to socio demographic characteristics

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<tr>
<th>Depression status</th>
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<td>Major depression</td>
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<td>79.2</td>
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**DISCUSSION**

This study has clearly shown that HIV causes major depression in HIV infected antenatal mothers. Experience of major depression was directly related to illiteracy, type of occupation, age and lower income status. In terms of order of birth, half of the respondents became pregnant for the second time in spite of knowing the chances of mother to child transmission of HIV. Such contraction requires immediate attention from the
health care providers and AIDS workers. This gap may be due to absence of effective intervention at the health setup or may be due to attitude of the women themselves. Forty four percent of children born to HIV infected mothers were low birth weight babies. Psychological disturbances i.e. experience of major depression coupled with poor socio-economic conditions could have impacted this.

Breast feeding was opted by 39.2% of respondents despite knowing the risk of mother to child transmission. Economic determinants coupled with cultural factors could have determined the choice of feeding. Though the study did not look at the cultural reasons, it was evident that the participants economical status did have a major role in the choice of feeding as close to one third of the respondents had income below INR 1500.

Discrimination owing to HIV status is still high among the participants. Participants who felt discriminated were more likely to experience major depression. Discrimination may include a broad range of harmful actions against individuals who are known or suspected of having HIV or AIDS (and/or their families), including rejection, exclusion from social or ritual events, gossip, ridicule, verbal harassment, abandonment, divorce, expulsion from their homes, removal of economic support, denial of property and, in some cases, physical violence. Likewise participants in this study who felt discriminated have experienced major depression.

Secondly the impact of disclosure also needs a close considering while trying to address the psychological disturbances among women. The negative consequences of disclosure are more frequently documented for women, and several studies show that it is among pregnant women that fears of abuse as a possible consequence of testing positive for HIV manifest more. This was observed among the respondents too as one third of women were asked to stay away from husband’s place. Furthermore, increase in incidence of 2nd pregnancy highlights the need for an appropriate, relevant and effective intervention package in the post natal period. First one is promotion of planned deliveries.

Promotion of planned deliveries

Increased incidence of 2nd pregnancy highlights the absence of unplanned pregnancy among the study community. In addressing the issue one, health care workers should provide necessary education, counseling and services on prevention of unwanted pregnancy. Presently, family planning program just looks at the number that could be achieved through permanent contraceptive measures. Permanent contraceptive methods are not yet popular among Indian women and it is considered as a right choice for women who are old enough not to give birth. Secondly, emergency contraceptives are not yet given enough attention. In addressing this issue, health care workers should develop culturally appropriate family planning methods.

Counseling and peer support groups

Counselling has been used to resolve issues with family and community members and to teach coping skills. Interventions studies suggest that counselling may reduce anxiety and distress, reduce negative consequences of disclosure and improve attitudes towards people living with HIV. Counselling and “mediated disclosure” can be used to help clients who test positive for HIV consider how to disclose their status to partners and others in a way that reduces risks to their physical safety and emotional wellbeing. As for as the quality of counselling services, women’s experiencing major depression was high in spite of the counselling services that they received from a counsellor. This clearly shows that there is inadequacy in the services provided by the counsellors. Currently, the quality of counselling services provided to the ANC mothers is not reported to be effective. Therefore, the counsellors should improve their quality of services that address the psychological needs of women. Counsellors should also be trained on various psychotherapeutic methods and tools.

Peer support groups have also been shown to benefit people living with HIV in terms of self-esteem, coping skills and social integration in a few situations. Therefore the researchers suggest that the counsellors can promote the concept of peer support groups as part of counselling services they offer.

Psychiatric intervention

Provision of services of a psychiatrist or psychiatric social worker can also be explored so that major depressions among women are identified early to initiate appropriate intervention.

Therefore, the researchers conclude that high level of major depression among ANC mothers needs immediate attention from health care workers.
Hence, ANC services should include referral mechanism to psychiatric interventions.

Simultaneously attempts should be made to improve the quality of services of counsellors and health care workers attached to HIV screening centers on planned delivery in both private and public health system.

CONCLUSION

This study finding clearly demonstrates that sizable percentage of pregnant mothers with HIV infection experience major depression. Therefore, quality of services of counsellors at ANC clinic and VCTCs need to be improved. In addition, the counsellors may be encouraged to perform periodical assessment of psychological needs of pregnant mothers. Further a comprehensive service package including referral for mental health services, commencing women on antenatal treatment, diagnosis and treatment of children born to pregnant women should be made available.

REFERENCES


Case Study

EXTRA-PULMONARY TUBERCULOSIS MIMICKING FRONTAL SINUSITIS

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2 Department of ENT, PGIMER, Rohtak

ABSTRACT

Tuberculosis of paranasal sinuses is very rare. It is usually secondary to pulmonary Tuberculosis. Among the Paranasal sinuses, maxillary sinus is the most common to be involved by tuberculosis. Frontal sinus Tuberculosis is very rarely seen. We report a case of extra-pulmonary Tuberculosis of frontal sinus presenting as mucocele in a 40 year old female who presented with a painless swelling. Computed Tomographic scan of Paranasal Sinuses revealed it to be a mucocele but Fine Needle Aspiration Cytology clinched the diagnosis. It was managed conservatively by Anti Tubercular Treatment.

INTRODUCTION

Tuberculosis (TB) of Paranasal Sinuses (PNS) is rare. The infection usually occurs secondary to pulmonary TB and reaches PNS via hematogenous route or lymphatics.1 The early features of TB of PNS are non specific and mimic chronic sinusitis thereby leading to delay in diagnosis and treatment. Diagnosis is challenging and can be confirmed only on histopathological examination. We report an unusual presentation of primary extra-pulmonary TB presenting as frontal sinusitis.

CASE REPORT

A 40 year old female presented with complaints of painless, progressive swelling over left orbit for 1 year. There were no complaints of headache or recurrent nasal discharge or nasal obstruction. Patient went to private practitioner for the above complaint 6 months back and underwent some surgical procedure, the details of which were not available. On clinical examination, a soft boggy swelling (approx. 2x1cm) was palpable in the superomedial aspect of left orbit with a healed scar on the overlying skin. The swelling was non tender and aspiration revealed a dry tap. Rest of the ocular examination was unremarkable. Nasal endoscopy was normal. A provisional diagnosis of left fronto-ethmoidal mucocele was made and CECT PNS was done. CECT PNS and orbit revealed enhancing soft tissue mass in the preseptal region in the superomedial aspect of left orbit with destruction of superomedial wall of left orbit (from previous surgery). Also, soft tissue opacification of the left frontal sinus was seen (Figures 1 & 2). Rest of the PNS were normal. FNAC from the swelling was done and was suggestive of features of tuberculosis (Figure 3). CXR was done and did not reveal any pulmonary infiltrates. ESR was raised but Montex Test was negative. Thus, a diagnosis of primary extra-pulmonary TB of frontal sinus was made and patient was started on Anti-tubercular treatment (ATT) with disappearance of swelling after 6 months of ATT.

DISCUSSION

With the advent of HIV infection, there has been a rise in extra-pulmonary TB1. Nasal TB is rare because of structure of the mucosa, respiratory movements of the cilia and bactericidal secretions. However, it can become infected either directly (primarily) through the air current by people sneezing or coughing or by direct inoculation by finger borne infections and by instrumentation.2 Primary TB of frontal sinus is rare.
Pathologically, three types of sinus TB have been described: In the first type, infection is confined to the mucosa only which presents a boggy, pale appearance. Purulent discharge is minimal, therefore diagnosis is difficult. The second type has bony involvement and fistula formation. Discharge is abundant and the tubercle bacilli are readily found. The third type is hyper-plastic type with the formation of tuberculoma. This is the rarest type.1 In our case, the disease was confined to mucosa as seen on CT. The bony defect was due to previous surgery and not a part of disease process.

The most common symptoms of tuberculosis of frontal sinus are: headache, fronto-ethmoid swelling, purulent secretions from nose, deteriorated sense of smell, and nasal bleeding.1 Since the early symptoms are non specific, patients are usually treated as chronic sinusitis.4 In our case, patient presented with swelling over the left orbit without any nasal complaints. On nasal examination, features suggestive of TB are: crusting, septal ulcer or perforation, granulations in the sinuses5 and pale mucosa. In our case, nasal examination was unremarkable. On clinical examination, it was thought to be a mucocele and CT revealed a soft tissue mass.

Diagnosis of TB sinus is challenging. It is based on histopathological examination. Sometimes, immune histochemical stains are required6 to establish the diagnosis and differentiate them from other granulomatous conditions. Common differential diagnosis of such lesions includes midline granulomas such as Wegener’s granulomatosis, leprosy, sarcoidosis, granulomatous syphilis, rhinoscleroma and rhinosporidiosis.

Treatment of TB PNS is medical with 6 months of ATT. Surgical treatment might be required in late presentations when patient presents with bony fistulae.

CONCLUSION

Frontal sinus TB is very rare. It is essential to have high index of suspicion for diagnosing such cases. Our case highlights the unusual presentation of frontal sinus TB. We also recommend that all samples from nose during surgery or suspicious on endoscopy must be subjected for histopathological examination.
REFERENCES
