

PREVALENCE OF DRUG RESISTANCE  
OF MYCOBACTERIUM TUBERCULOSIS  
IN HARAR  
(EASTERN ETHIOPIA)

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Prevalence of Initial and Acquired Resistance of  
*Mycobacterium Tuberculosis*

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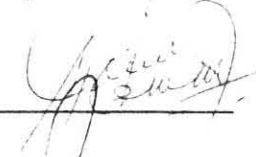
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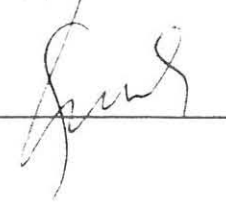
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**LIST OF ABBREVIATIONS**

1. AIDS - Acquired Immuno-Deficiency Syndrome
2. DCH - Department of Community Health
3. E - Ethambutol
4. H - Isoniazid
5. HIV - Human Immuno Deficiency Virus
6. NRIH - National Research Institute of Health
7. NTCP - National Tuberculosis Control Programme
8. R - Rifadin
9. SM - Streptomycin
10. TB - Tuberculosis
11. Th - Thiacetazone

**ABSTRACT**

A hospital based cross sectional study was carried out in order to describe the magnitude of anti-tuberculosis drug resistance and identify the risk factors associated with it.

The study was carried out in Harar tuberculosis centre which is the major tuberculosis treatment centre in eastern Ethiopia. A total of 338 smear/culture positive patients were enrolled in the study between October 10, 1994 and January 20, 1995. Exposure status was determined through interview; drug resistance and HIV status were determined through laboratory investigation.

The overall prevalence of resistance to one or more anti-tuberculosis drugs was 126/338 (37.3%). Initial resistance was 82/252 (32.5%) while that of acquired was 44/86 (51.2%). History of previous treatment was the strongest predictor of anti-tuberculosis drug resistance ( $p < 0.005$ ). HIV infection was found to be an important predisposing factor in those who had history of previous treatment ( $p < 0.05$ ).

The prevalence of drug resistance is high in Harar. There is a need for periodic national drug resistance survey. Implementation of the WHO recommended supervised treatment with multi-sectoral approach is suggested.

## INTRODUCTION

Tuberculosis is an ancient disease that has long been a major public health problem. Despite efforts in the past to control the disease, pulmonary tuberculosis has remained an important health problem world-wide. Especially in developing countries, tuberculosis has continued to be a major health threat (1).

Today, two new problems threaten the control of tuberculosis in general: the epidemic of human Immunodeficiency virus (HIV) infection and drug resistance. HIV infection is the greatest risk factor so far identified for latent tuberculosis infection to progress to active disease. The epidemic has significantly affected the epidemiological situation of tuberculosis in both developed and developing countries. Especially in those developing countries where HIV infection and tuberculosis infection are more prevalent, HIV epidemic has had a considerable impact on tuberculosis control programmes (2).

The resurgence of tuberculosis has been further aggravated by the spread of anti-tuberculosis drug resistant bacilli. Although drug resistance is not a new problem, an increasing trend has been observed since the HIV era. Epidemics of drug resistant tuberculosis are

noted even in developed countries including Europe and the United States where the disease was no longer considered a public health problem and funding of tuberculosis programme and research activities had been practically abandoned (3-6).

Anti-tuberculosis drug resistance may be classified into two major groups: Primary resistance or secondary (acquired) resistance. The first is due to random mutation while the later is a result of inadequate treatment. The term initial resistance is used when strains can not be classified as primary or secondary (7,8).

In many developing countries, where there are poor tuberculosis control programmes, increased prevalence of drug resistance has been noted (1,2,5).

The epidemic of HIV infection has also affected both the diagnosis of pulmonary tuberculosis and the treatment of multi-drug resistant cases. It has been noted that the treatment of multi-drug resistant cases is very expensive and the outcome of treatment is usually unsatisfactory (1-3,9).

In Ethiopia, the tuberculosis control programme was not strengthened and activities were limited to the tuberculosis centres for the last three decades. Although the National Tuberculosis Control Programme was officially established in 1976, it was not functioning

very well. This was primarily due to the limited resource allocated to this programme. For the last few years, anti-tuberculosis drug resistance was not considered a major problem in this country. The few studies carried out have tried to show the drug resistance pattern in the tuberculosis centres. Although periodic drug resistance survey was recommended, few attempts have been made and the studies were limited to Addis Ababa tuberculosis centre (10).

This study was conducted in Harar (eastern Ethiopia) where one of the tuberculosis centres is located. This centre serves as the major tuberculosis treatment centre in eastern Ethiopia. The centre is not involved in any of the tuberculosis control activities except in the treatment of cases (out-patient and in-patient). Treatment is not supervised and there is no any mechanism for defaulter tracing. Repeated shortage of anti-tuberculosis drugs and reagents was observed. Additionally, drugs are smuggled from Djibouti to Dire Dawa and patients are obliged to buy from the private sector with a very high price. War, drought, and the frequent in and out-migration of the population have affected the tuberculosis control in this area. For the reasons mentioned above tuberculosis has remained one of the three leading causes of morbidity and mortality persistently.

Since Ethiopia is in the process of reorganizing its National Tuberculosis Control Programme, the investigation of the problem of drug resistance will be of great value in the provision of base line information. Unlike previous studies, this study has looked at issues of drug resistance in the presence of HIV epidemic. Since the infectious cases of pulmonary tuberculosis (i.e. smear positive cases) are the main targets of public health measures, this study has focused on the smear positive pulmonary tuberculosis patients. The findings of the study will be of help to those who are engaged in tuberculosis and AIDS control programmes and those who are involved in the treatment of tuberculosis.

## LITERATURE REVIEW

### 1. Magnitude of tuberculosis

(A) **Global:** About 1700 million people, i.e. one third of the human population, are infected with mycobacterium tuberculosis while the disease prevalence is estimated to be 20 million. The global annual incidence is 8 million cases. Tuberculosis is the largest cause of death from a single infectious agent in the world, killing nearly 3 million people per year; 90% of them in developing countries (1,2,4).

According to WHO, this death toll represents 25% of avoidable adult deaths in developing countries. WHO has estimated that more than 30 million deaths will occur in the next decade and tuberculosis deaths are expected to increase to over 4 million annually (11). In the United States there are in excess of 20,000 reported cases and over 1700 reported deaths per year attributable to tuberculosis. In New York city, the incidence of reported tuberculosis increased 132% from 1980 through 1990. Similar increase was noted in Europe (Austria, Denmark, Ireland, Italy, The Netherlands, Norway, Spain, and United Kingdom). In developing countries more than 3 million new cases of smear positive tuberculosis occur annually (12).

Morbidity and mortality are concentrated in young adults (age group 15-49 years). Since the deaths occur

among young adults upon whom younger and older persons often depend for support, the social and economic impact of tuberculosis is tremendous. The above condition is worse in developing countries where the age dependency ratio is usually high.

**(B) Regional:** In Africa 171 million people are infected with mycobacterium tuberculosis. Annually, 1.4 million new cases and 660,000 deaths are estimated to occur. The annual risk of infection is 1.5 - 2.5% (13-15).

**(C) Ethiopian situation:** According to the National Tuberculin survey done between 1987 and 1990, the prevalence of tuberculosis is estimated to lie between 180,000 and 308,000 with an annual incidence of 90,000 and 154,000. Of these 41,000 to 70,000 are infectious cases. It was documented that 20,000 to 35,000 infectious cases of tuberculosis die each year. This survey was conducted when the civil war in Ethiopia was at its peak. Therefore, areas with high prevalence of tuberculosis were not included. Probably that is the reason why the reported annual risk of infection (1.5%) was lower than the one reported previously (3.0%). Additionally, it is unlikely that there was a significant intervention during the last 12 years

(1978-1990). Reports from health institutions indicate that tuberculosis is among the 10 top causes of out patient visits. It is the first cause of hospital

admission and among the leading causes of hospital death (16).

## **2. Tuberculosis and HIV infection**

The HIV pandemic has led to a dramatic increase in the number of tuberculosis cases worldwide (1-15). HIV infection is said to facilitate tuberculosis infection by destroying the host defence mechanism (cell mediated immunity) which is the main defence mechanism by which the human body protects itself from tubercle bacillus. Tuberculosis has been identified as the first manifestation of HIV infection in HIV infected patients. This is because *Mycobacterium tuberculosis* is more virulent than other HIV associated pathogens such as *Pneumocystis carinii* and *Mycobacterium avium* complex and is more likely to cause disease at an earlier stage of immunodeficiency (1,17). It has been postulated that tuberculosis infected persons who are also infected with HIV have a very high chance of developing active tuberculosis. Studies in Cote d' Ivoire, Zaire and Rwanda have shown that the risk of developing active tuberculosis is 11-26 times higher in HIV infected persons than those who are not infected with HIV (1,17-19). It is estimated that 4 - 5 million people are already infected with both latent tuberculosis and HIV, giving them a high risk for developing active

tuberculosis (20).

In many developing countries, high HIV sero-prevalence was documented among patients presenting with active tuberculosis. Data from several African countries and Haiti (collected between 1985 and 1990) show that HIV sero-prevalence is high in tuberculosis patients, ranging from 17 to 66% (2). In contrast, in various studies in the USA, the median sero-prevalence in patients with TB was 3.6%. Among homeless tuberculosis patients, HIV seroprevalence has risen up to 43% in 1992 (2,17,21,22).

### **3. Anti-tuberculosis drug resistance**

The control of tuberculosis has been complicated by the wide-spread of resistant tubercle bacilli. It has affected both developing and developed countries. If the spread continues, tuberculosis may become uncontrollable (5).

Drug resistance may be primary or secondary (acquired). Patients who have never been treated for tuberculosis but who are found to have drug resistant tubercle bacilli, are said to have primary drug resistance. Patients with a history of previous treatment found to have a resistant strain are defined as having secondary or acquired resistance. For technical reasons, it is not always possible to determine whether a patient had been exposed to anti-tuberculosis drugs or not.

Therefore, it has been suggested that the term initial resistance should be used instead of primary resistance (21). Initial resistance refers to drug resistance in patients who claim never to have received previous anti-tuberculosis treatment. Initial resistance represents to a varying degree, a contamination of primary resistance (the result of infection with a resistant strain that progressed to clinical tuberculosis) with acquired resistance resulting from undisclosed previous treatment (8).

High initial drug resistance reflects poorly functioning tuberculosis control programme in the population in the past. On the other hand, high acquired resistance indicates poor individual compliance, or an inadequately conducted or designed tuberculosis treatment programme and reflects a poorly functioning national tuberculosis programme at the present time (7,8,21).

Drug resistance of mycobacterium tuberculosis develops in two ways. The first is by the selective growth of resistant mutants evolving in a wild population when exposed to an amount of drug sufficient to inhibit growth of sensitive organisms. Tubercle bacilli have spontaneous predictable chromosomally borne mutations that confer resistance to anti-microbial agents. The emergence of drug resistance represents the survival of random pre-existing mutations, not a change caused by

exposure to the medication. The British Medical Research Council's streptomycin trial revealed that in each wild strain of tubercle bacilli, approximately 1 out of every  $10^6$ - $10^7$  organisms is spontaneously resistant to at least 1 of the known drugs. Resistant organisms to isoniazid could be encountered in a mycobacterial population of  $10^6$ . Patients with cavitary pulmonary lesions may harbour  $10^6$ -  $10^9$  tubercle bacilli (7,21,23).

The second route of development of resistance is the selection of resistant organisms by intermittent courses of anti-tuberculosis medications or as a result of inadequate treatment. Patients who take drugs irregularly or patients who had inappropriate prescriptions of anti-tuberculosis drugs have an increased chance of developing acquired resistant tuberculosis and becoming chronic excretors of resistant bacilli (5,7,21,23).

Drug resistance arises when treatment is unsupervised, when drugs are freely available on the private market and when fixed dose combinations are not available. In the United States, immuno-compromised persons living in over crowded conditions such as hospitals, prisons, homeless shelters, and residential drug treatment programmes were found to be at greater risk (24).

Emergence of resistance to isoniazid and rifampicin is a public health concern, since these drugs are

essential components in the treatment and control of tuberculosis. Isoniazid resistance is important for two reasons: The first is that isoniazid is a critical component of both the standard and short course chemotherapy, and secondly isoniazid resistance is usually associated with resistance to other anti-tuberculosis drugs such as rifampicin. This is reflected in the observation that multiple drug resistant isolates are nearly always resistant to isoniazid and isolated isoniazid resistance is relatively uncommon (25).

In United States the prevalence of drug resistant organisms among patients with pulmonary tuberculosis has steadily increased from 2% to 9% in the last three decades. During the period 1982-1991, the prevalence of resistance in patients who had previous history of anti-tuberculosis treatment has ranged 13% to 59%. Primary resistance to one or more anti-tuberculosis drugs increased from 10% in 1982 to 23% in 1991. Resistance to isoniazid and rifampicin increased from 9% to 15% and from 3% to 9% respectively (23,24). During the second half of the 1980s and in the early 1990s single and multiple resistance to streptomycin and isoniazid were the most prevalent form throughout Latin America. Overall initial resistance was 11.6% to streptomycin, and 6.5% to isoniazid (26).

A study done in Turkey (between January 1992 and

December 1992) showed the over all resistance to one or more drugs to be 35.5%, with initial resistance 26.6 % (140 of 525) and acquired resistance 53.4%(139 of 260). Acquired resistance to rifampicin was the most frequent (36.2%) followed by streptomycin 31.9%, and isoniazid 30%. According to this study initial resistance was 16.4% to 1 drug, 7.7% to 2 drugs, 1.2% to 3 drugs and 1.3% to 4 drugs. Similarly acquired resistance was found as 18.7% to 1 drug, 19.3% to 2 drugs, 9.6% to 3 drugs and 5.8% to 4 drugs (27).

In Korea (1992) a significant difference in the prevalence of initial resistance was observed between urban and rural patients. Initial resistance was much higher among urban patients than rural. The main reason that initial resistance is high among urban patients may be that urban patients have better access to drugs than the rural patients. In this study higher prevalence was also found among younger patients (<30 years) than older patients (59 and over) (28). Initial resistance may provide useful information on the type of chemotherapy that should be used for the treatment of patients who come to health institutions for the first time, and may also serve as a useful parameter in the evaluation of current and past chemotherapy programmes.

In India (1988), Travedi and Desai showed that initial resistance is increasing over the years (29).

Similarly a study done in 1993 has shown that the proportion of resistant cultures increases as the amount of drugs consumed increases, being highest among those who have failed or relapsed, after adequate chemotherapy. In this study initial resistance to rifampicin was 12% . It is possible that many patients had a concealed history of chemotherapy, or that they had been taking rifampicin from private practitioners with out being aware of the fact (30). Researchers have noted that although the number of deaths are reduced in poorly controlled treatment programmes, the number of chronic excretors tends to rise.

Between 1986 and 1988, in Riyadh (Saudi Arabia) the prevalence of primary resistance was 11.5% . According to this study resistance to isoniazid was the commonest. A similar study done in South Africa demonstrated that the prevalence of initial drug resistance was 12.7% in 1983-84 and 10.7% in 1988-89 (31,32) .

A cross sectional study done in Abidjan, Ivory Coast (West Africa) showed that initial resistance to isoniazid, streptomycin and rifampicin was 17%, 3% and 2% respectively (33). In Ghana, a hospital based study carried out between July 1985 and 1987 showed that there was a high resistance to isoniazid and streptomycin 27% and 23.5% respectively. Double resistance to streptomycin and isoniazid combined was 16% while

resistance to three drugs was 5% (34). In this study resistance to other mycobacterium other than mycobacterium tuberculosis was included. The diagnosis of pulmonary tuberculosis using conventional sputum examination has become a challenging problem in the treatment programmes of tuberculosis. This problem is apparent in developing countries where sputum examination is the mainstay of diagnosis of pulmonary tuberculosis. Different studies have noted that quite a significant number of pulmonary tuberculosis patients with HIV infection are smear negative on sputum examination (2,35). In Zambia, a study done on 144 pulmonary tuberculosis patients (confirmed by a sputum culture) showed that only 57% of HIV sero-positives had positive sputum smear, as compared with 76% in HIV sero-negatives. The study found that bacillary load was lower in the sputum of HIV positives than of HIV negative tuberculosis patients (36). On the contrary, in Haiti it was demonstrated that sputum examination results are quite comparable in both HIV positive and negative patients especially during the early phases of HIV infection i.e. before the immune system is severely compromised (37). According to the available information, the pattern of drug resistance increasing in this country. High default rate (more than 80%) (38), availability of anti-tuberculosis drugs on the open market, and improper

selection of drugs for the treatment of drug resistant tuberculosis are expected to increase the pool of resistant infection in the population. As elsewhere in the developing countries, the epidemiology of tuberculosis has been affected by the growing epidemic of HIV infection. According to a study done in Southern Ethiopia (1994), HIV sero-prevalence among tuberculosis patients was 44.4% (39).

A study done on 184 isolates of mycobacterium tuberculosis from Addis Ababa Tuberculosis Centre (1978) showed that resistance to isoniazid, thiacetazone and streptomycin was 46%, 46%, and 29% respectively. Double resistance to isoniazid + thiacetazone, and isoniazid + streptomycin was reported to be 20% and 28%. Triple resistance to isoniazid + streptomycin + thiacetazone was 16%. All the above isolates were from treatment failure and relapse cases (40).

A similar sensitivity study done in 1984, from the same Tuberculosis Centre, revealed that primary resistance to isoniazid, streptomycin and thiacetazone was 14.8%, 4.9% and 3.8% respectively (41). In 1986, a study was done to determine the prevalence of anti-tuberculosis drug resistance by involving all the three tuberculosis centres (Addis Ababa, Asmara and Harar) in Ethiopia. The study showed that primary resistance to one or more major anti-tuberculosis drugs was 15.2%.

Resistance to isoniazid alone was 12%. No resistance has been observed for ethambutol and pyrazinamide (42). The most recent published data on primary resistance was done in Sidamo hospital in 1989. According to this finding, primary resistance to one or more anti-tuberculosis drugs was 7.6% (43).

## OBJECTIVES

### General:

To determine the magnitude of drug resistant mycobacterium tuberculosis to five major anti-tuberculosis drugs in Harar (Eastern Ethiopia) and, to identify factors associated with it.

### Specific:

- 1- To determine the prevalence of initial and secondary resistance among smear positive pulmonary tuberculosis cases.
- 2- To determine the association between HIV status and drug resistance in smear positive cases.
- 3- To examine the association of drug resistance with other socio-demographic, medical, etc., factors.

## MATERIALS & METHODS

1. *AREA PROFILE:* Harar is located 525 km from Addis Ababa. It serves as the capital city of region 13. Region 13 consists of 4 Woredas i.e. 19 urban dwellers associations of Harar city and 17 peasant associations around the city. The total population of the region is 166,909. Of these, 55.5% reside in Harar town. The male to female ratio is 94:100. The population density is found to be 490.2 per sq.km. Agriculture is the economic foundation of the rural population. The urban population is engaged in retail trade, manufacturing, governmental and other civilian activities.

The region has three civilian and two military hospitals, of which the tuberculosis centre is one. In addition, there are three urban and two rural clinics.

The doctor to population ratio is 1: 5,215. The health service accessibility (within 10 km radius) is 71.5% and the per capita health expenditure is 7.3 Birr. These findings are better by far than the national figures.

According to the disease profile of the area (Mitike G. and Belachew A., 1994), tuberculosis has been consistently among the 10 top diseases. In 1993 /94, it stood third in the hospital out-patient visits and second in hospital admission and death.

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## 2. OPERATIONAL DEFINITIONS

**Initial resistance:** Is defined as the presence of drug resistance to one or more anti-tuberculosis drugs in a patient who denied previous history of treatment.

**Secondary (Acquired) resistance:** Is defined as a resistance to one or more anti-tuberculosis drugs in those who had previous history of anti-tuberculosis treatment.

**New case:** A patient who has never taken anti-tuberculosis drugs for more than one month.

**Smear positive:** A patient with two sputum specimens positive for acid fast bacilli by microscopy.

**Smear negative:** A patient with two sputum specimens negative for acid fast bacilli by microscopy.

**Defaulter:** A 3 or more days of consecutive absence in the intensive phase and a 2 months failure to collect drugs in the continuation phase.

**Relapse:** A patient presenting with smear positive pulmonary tuberculosis after having been declared "cured" following completion of a course of tuberculosis chemotherapy sometimes in the past.

**A chronic case:** A patient who has been discharging tubercle bacilli for more than 2 years or who is still discharging tubercle bacilli after having completed a re-treatment regimen.

**Treatment failure:** Patients who do not show sputum

conversion 5 months after the start of treatment of chemotherapy, be it short course or " standard ".

**Multi-drug resistance strains:** *Mycobacterium tuberculosis* resistant to isoniazid and rifampicin, with or without resistance to other drugs.

3. *DESIGN:* This is a hospital based, cross-sectional study with internal comparison where three hospitals (TB centre and two general hospitals) were involved. The source population includes infectious cases of pulmonary tuberculosis in Eastern Ethiopia while the study population included all smear positive pulmonary tuberculosis cases attending the out-patient departments of the three hospitals in Harar town.

A total of 418 cases were enrolled between October 10, 1994 and January 20, 1995. Most of these patients were self referrals to the Harar tuberculosis centre which is the major tuberculosis treatment centre in Eastern Ethiopia. Patients were classified in two groups: those pulmonary tuberculosis patients who denied any history previous treatment were taken as new cases and resistant tubercle bacilli isolated from these patients were considered to be initial resistance, while those patients with previous history of anti-tuberculosis treatment were considered as old cases and drug resistance reported on the isolates was considered as acquired (secondary) resistance.

4. *INCLUSION & EXCLUSION CRITERIA*: Smear positive cases, with or without previous history of anti-tuberculosis treatment were included. Smear positive cases, who declined to participate in the study, all smear negative cases, and patients with extra pulmonary tuberculosis were excluded from the study.

5. *VARIABLES*: Initial and acquired drug resistance are the major outcome (dependent) variables while previous history of treatment and status of HIV infection are the most important exposure (independent) variables addressed. Other independent variables included are:

(a) **Socio-demographic**: Age, sex, ethnicity, educational status, religion, occupation, place of residence, distance from tuberculosis centre, economic standard, number of family members.

(b) **Medical**: presence of contact history with a known tuberculous patient or with a chronic cough in the same family.

6. *DATA COLLECTION TECHNIQUES*: Training was given for both the interviewers and the laboratory technicians. The questionnaire was translated into Amharic and was pretested.

Exposure status to anti-tuberculosis drugs and resistance to anti-tuberculosis drugs were determined as follows: For all suspected tuberculosis patients, visiting the out-patient departments of the three

hospitals, a brief orientation was given about the procedure of sputum collection i.e. the amount required, the quality of the sputum, how to produce deep sputum, etc. Patients were classified as smear negative or positive after two consecutive smear examinations with Ziehl Neelsen stain. After carefully explaining the purpose of the study an informed consent was obtained from each candidate. Exposure status was determined using an in-depth interview and drug resistance was determined using laboratory findings. In order to maintain confidentiality, a different code for each smear positive tuberculosis patient enrolled in the study was used. The same codes for both sputum and blood specimens collected from one patient were given.

Collected sputum and blood specimens were stored as follows: Sputum specimens were collected from each patient using a sterilized standard container. Sputum cups were tightened with an adhesive plaster in order to prevent specimen leakage and were kept in a refrigerator at 4° C. Collected blood specimens were centrifuged after being kept in a rack for one hour. After separating the serum, specimens were kept in a deep freeze. Both serum and sputum specimens were transported to the National Research Institute of Health (Addis Ababa) within 12 days of collection. Cold boxes were used during transport and all specimens were sent by air to Addis Ababa. At the

NRIH, Acid fast staining (Ziehl Neelsen) was done before processing the specimens for culture. The number of bacilli were quantified as scanty (+), moderate (++) and many (+++). Then, sputum samples were decontaminated and centrifuged. The sediment from each specimen was inoculated on tubes with Loewenstein-Jensen medium. The cultures were incubated at 37° C until growth of colonies was observed. The cultures were inspected after 48 hours, and then weekly. Each isolate strain was examined for morphology, pigmentation and the date and appearance of the colonies was noted. Identification was made based on internationally recommended procedures. After 9 weeks (63 days), specimen tubes which did not show growth were said to be negative or contaminated. The procedure of drug susceptibility testing was done based on the simplified variant of the proportion method of Canetti et al (44). The tests were done in Lowenstein-Jensen medium. Susceptibility testing was done on 5 major anti-tuberculosis drugs isoniazid (H), thiacetazone (Th), ethambutol (E), streptomycin (SM), and rifampicin (R). Resistance was expressed as the percentage of colonies that grow on the following critical concentrations that are used to separate resistant strains from sensitive ones: 0.2 µg/ml for isoniazid, 2 µg/ml for ethambutol, 4 µg/ml for dihydrostreptomycin, 40 µg/ml for rifampicin and 2 µg/ml for thiacetazone. Factors that could affect

the sensitivity tests such as inoculum size, composition of medium, incubation period and reading of test were carefully controlled.

Susceptibility of the strains was determined using the proportion of bacilli resistant to the specific drug in comparison with growth on a specific control using international criteria.

Resistance was defined as 1% or more growth for H, R, E and 10% for SM and Th (8,21,44).

Serum samples were tested for the presence of HIV antibody by a competitive recombinant Enzyme Linked Immuno-Sorbent Assay (Wellcozyme, Wellcome Diagnostics, Dartford, Kent UK) and antiglobulin recombinant ELISA assay. ELISA<sub>3</sub> was done on serum samples which showed equivocal results. All tests were performed in the AIDS laboratory of the NRIH. WHO recommendations and kit manufacturers instructions were strictly adhered (45). HIV test results were not known by name to any of the peripheral and central laboratory technicians or interviewers so that confidentiality was maintained. Throughout this text HIV positive mean HIV<sub>1</sub> seropositivity since there are no reports of HIV<sub>2</sub> in Ethiopia so far.

From previous studies the expected prevalence of initial drug resistance of tubercle bacilli ranges between 7.6% and 15.2% and that of acquired (secondary)

drug resistance ranges between 20% and 30%. Using a 15% disease prevalence in un-exposed group with 3:1 ratio of unexposed to exposed at  $\alpha = 0.05$ , a sample of 336 would be enough to detect an odds ratio of 2.43 with 80% power. Sample size calculations were made using EPI-INFO statistical package.

7. *QUALITY CONTROL*: For quality control a three days training of both laboratory technicians and interviewers was made as to how enrol, investigate and interview patients. Both questionnaires and specimen processing (collection, storage and transport) were pretested. Nurses were used for interviewing patients while the status of the laboratory technicians was the same in the three hospitals. Interviewers were visited daily and necessary corrections were made on the spot i.e., before patients collect their drugs. Culture and sensitivity were done in the central tuberculosis laboratory of the National Research Institute of Health. The laboratory technician involved had a 20 year of experience and supervision was made by a senior microbiologist.

8. *DATA PROCESSING AND ANALYSIS*: Data collected from interviews and laboratory findings were analyzed using EPI-INFO (version 5.0) and SAS (version 6.03) statistical packages. Chi-square ( $\chi^2$ ) test, was calculated to detect statistically significant differences. Odds ratio was used to measure the degree of association. A probability

of  $< 0.05$  was considered to be significant. Data are presented in the form of frequency and contingency tables.

9. *ETHICAL CONSIDERATIONS:* Before obtaining a verbal consent from the patients involved in the study, the following information was given to the patient: First an explanation was given about the importance of the study and why the test has to be carried out. They were told that procedures are safe and sterilized disposable needles and tubes (vacuutainer) will be used. In addition, they were informed that the tests will be carried out in a laboratory with a high quality of services, confidentiality will be maintained and only codes will be used instead of names. Finally they were told that they have the right to refuse.

For those who needed to know the HIV test results counsellors were arranged in the three hospitals involved in the study. All smear positive patients were given health education and were started on anti-tuberculosis treatment.

## RESULTS

A total of 418 smear positive pulmonary tuberculosis patients were enrolled in the study between October 10, 1994 and January 20, 1995. Of these, sputum cultures were positive in 338 (80.9%) specimens. The rest were either contaminated or did not show growth. The characteristics of the 80 patients with contaminated or negative cultures showed no significant differences with those with positive cultures. Of the 338 culture positive cases involved in the analysis, 195 (57.7%) were males while 143 (42.3 %) were females. The mean age was 27.7 years with a standard deviation (SD) of 10.5 years and an age range of 7-70 years. 52.1% were rural patients and farmers constituted 50.9% of the total. 58.9% of the patients have come from different districts of East Hararge, Dire Dawa and Ogaden regions. The remaining 41.1% were from the same district which includes Harar town and vicinity, located within 50 Kilometres from the tuberculosis centre (Table 1). Of the total culture positive patients 86 (25.4%) have had history of previous anti-tuberculosis treatment, while 252 (74.6%) denied previous history of treatment with anti-tuberculosis drugs.

The overall resistance to one or more anti-tuberculosis drugs was 37.3% (126/338). Resistance to one or more anti-tuberculosis drugs was 32.5% (82/252) in

those who denied previous treatment (initial resistance) and 51.2% (44/86) in those who had previous treatment (acquired resistance) (table 2). No statistically significant association was found between drug resistance and socio-demographic factors: age, sex, address (rural or urban), area of residence, ethnicity and level of education. Although a higher percentage (40.6%, 28/69) of drug resistant cases were HIV positive; as compared to 36.4% (98/269) in HIV negatives, the association was not found to be statistically significant (OR = 0.89, 95% CI = 0.54, 1.47). Previous history of anti-tuberculosis treatment was found to be an important predisposing factor for drug resistance (OR = 2.13, 95% CI = 1.25, 3.64)  $p < 0.005$ .

The distribution of drug resistance (initial and acquired) was further elaborated by type of drugs, and their combinations (table 3). Resistance was described as single, double and triple drug resistance. In this study resistance to streptomycin, isoniazid and the combination of isoniazid + streptomycin, isoniazid + rifampicin was significantly higher among old cases than new cases.

The relationship between initial resistance and selected risk factors which include socio-demographic factors is shown in table 3. No statistically significant association was found between initial anti-tuberculosis drug resistance and socio-demographic

factors: sex, address (rural or urban), area of residence (in-district or out-district) and crowding. Although not significant, an increasing trend of drug resistance was observed with increased age ( $p$  for trend = 0.56). The proportion of patients who were drug resistant was higher in HIV negatives (72/208; 34.6%) as compared to HIV positives (10/44; 22.7%). The association was not found to be statistically significant (OR=0.56, 95% CI=0.24,1.26). Table 5 shows the relationship between acquired drug resistance and selected risk factors. There was no significant association between drug resistance and sex (OR = 0.90, 95% CI = 0.35,2.30). The proportion of drug resistance was lower in urban (46.0%) than rural (58.3%), but the association was not found to be significant (OR = 0.61 CI = 0.23,1.59). When HIV status was analyzed for secondary drug resistance, HIV positive tuberculosis patients were found to be 3.5 times at risk in having drug resistance than HIV negatives. The association was found significant (OR = 3.46, 95% CI 1.13,10.1)  $p < 0.05$ . Although not significant, HIV positives were more defaulters (9/15; 64.3%) than HIV negatives (15/37; 40.5%) (OR=2.64, CI= 0.63,11.94). Although not significant, higher prevalence of drug resistance was observed in treatment failures (12/21; 57.1%) and relapse cases (8/14; 57.1%) than defaulters (24/51; 47.1%).

**Table 1**      **Characteristics of the study population,  
Eastern Ethiopia, 1994/95.**

| <b>variable</b>             | <b>number<br/>(N=338)</b> | <b>percent</b> |
|-----------------------------|---------------------------|----------------|
| <b>Age</b>                  |                           |                |
| 7-14                        | 18                        | 5.3            |
| 15-29                       | 171                       | 50.6           |
| 30-44                       | 123                       | 36.4           |
| 45+                         | 26                        | 7.7            |
| <b>Sex</b>                  |                           |                |
| male                        | 195                       | 57.7           |
| female                      | 143                       | 42.3           |
| <b>Ethnicity</b>            |                           |                |
| Oromo                       | 216                       | 63.9           |
| Amara                       | 86                        | 25.4           |
| other                       | 36                        | 16.7           |
| <b>Address</b>              |                           |                |
| rural                       | 176                       | 52.1           |
| urban                       | 162                       | 58.9           |
| <b>Education</b>            |                           |                |
| do not read or write        | 203                       | 60.1           |
| read and write              | 3                         | 0.9            |
| formal education            | 132                       | 39.0           |
| <b>Family income (Birr)</b> |                           |                |
| <105                        | 288                       | 85.2           |
| 105-300                     | 37                        | 10.9           |
| >300                        | 13                        | 3.8            |
| <b>Crowding index</b>       |                           |                |
| 1-2.99                      | 84                        | 24.9           |
| 3-5                         | 122                       | 36.1           |
| >5                          | 132                       | 39.1           |
| <b>Previous treatment</b>   |                           |                |
| yes                         | 86                        | 25.4           |
| no                          | 252                       | 74.6           |
| <b>HIV status</b>           |                           |                |
| positive                    | 69                        | 20.4           |
| negative                    | 269                       | 79.6           |

**Table 2** The distribution of anti-tuberculosis drug resistance in selected risk factors, Eastern Ethiopia, 1994/95.

| Resistance to one or more drugs |            |                   |                   |           |
|---------------------------------|------------|-------------------|-------------------|-----------|
| factor                          | pop<br>(n) | resistant<br>n(%) | OR (95% CI)       | p (trend) |
| <b>Age(yr)</b>                  |            |                   |                   |           |
| 7-14                            | 18         | 8 (44.4)          | 1*                |           |
| 15-29                           | 171        | 57 (33.3)         | 0.63 (0.21,1.85)  |           |
| 30-44                           | 123        | 50 (40.6)         | 0.86 (0.29,2.58)  |           |
| 45+                             | 26         | 11 (42.3)         | 0.95 (0.48,1.89)  | *         |
| <b>Sex</b>                      |            |                   |                   |           |
| female                          | 143        | 51 (35.7)         | 1*                |           |
| male                            | 195        | 75 (38.5)         | 1.13 (0.70,1.18)  |           |
| <b>Address</b>                  |            |                   |                   |           |
| urban                           | 162        | 54 (33.3)         | 1*                |           |
| rural                           | 176        | 72 (40.9)         | 1.38 (0.87,2.21)  |           |
| <b>Ethnicity</b>                |            |                   |                   |           |
| Oromo                           | 216        | 79 (36.6)         | 1*                |           |
| Amhara                          | 86         | 34 (39.5)         | 1.02 (0.63,1.62)  |           |
| other                           | 36         | 13 (36.1)         | 0.88 (0.51,1.62)  |           |
| <b>Education</b>                |            |                   |                   |           |
| illiterate                      | 203        | 79 (38.9)         | 1*                |           |
| read & write                    | 3          | 2 (66.6)          | 1.71 (0.20,12.88) |           |
| formal educ                     | 132        | 45 (34.1)         | 1.96 (0.22,15.01) |           |
| <b>Previous treatment</b>       |            |                   |                   |           |
| no                              | 252        | 83 (32.9)         | 1*                |           |
| yes                             | 86         | 44 (51.2)         | 2.13 (1.25,3.64)  |           |
| <b>HIV status</b>               |            |                   |                   |           |
| negative                        | 269        | 98 (36.4)         | 1*                |           |
| positive                        | 69         | 28 (40.6)         | 1.19 (0.67,2.21)  |           |
| <b>Contact history</b>          |            |                   |                   |           |
| yes                             | 110        | 43 (39.1)         | 1*                |           |
| no                              | 228        | 82 (36.0)         | 0.88 (0.54,1.44)  |           |
| <b>Total</b>                    | <b>338</b> | <b>126 (37.3)</b> |                   |           |

Note: Formal education means elementary, high school, 12+

\* = Trend was not found statistically significant

(P = 0.39)

OR = Odds Ratio

CI = Confidence Interval

**Table 3** The distribution of single, double and triple drug resistance, Eastern Ethiopia, 1994/95.

| drug(s)                          | Resistance              |                         |
|----------------------------------|-------------------------|-------------------------|
|                                  | Initial (N=252)<br>n(%) | Acquired (N=86)<br>n(%) |
| <b>One drug</b>                  | <b>82 (32.5)</b>        | <b>44 (51.2)</b>        |
| H                                | 54 (21.4)               | 38 (44.2)               |
| Th                               | 16 (6.3)                | 7 (8.1)                 |
| E                                | 1 (0.4)                 | 0 (0.0)                 |
| SM                               | 51 (20.2)               | 27 (31.4)               |
| R                                | 4 (1.6)                 | 5 (5.8)                 |
| <b>Two drugs</b>                 | <b>35 (13.9)</b>        | <b>26 (30.2)</b>        |
| H+Th                             | 11 (4.4)                | 5 (5.8)                 |
| R+H                              | 1 (0.4)                 | 3 (3.5)                 |
| SM+H                             | 25 (9.9)                | 20 (23.2)               |
| SM+Th                            | 3 (1.2)                 | 2 (2.3)                 |
| R+SM                             | 1 (0.4)                 | 3 (3.5)                 |
| <b>Three drugs</b>               | <b>4 (1.6)</b>          | <b>2 (2.3)</b>          |
| H+Th+SM                          | 4 (1.6)                 | 2 (2.3)                 |
| R+SM+Th                          | 0 (0.0)                 | 2 (2.3)                 |
| R+SM+H                           | 0 (0.0)                 | 0 (0.0)                 |
| <b>Resistance to one or more</b> | <b>82 (32.5)</b>        | <b>44 (51.2)</b>        |

Note: H=isoniazid, Th=thiacetazone, E=ethambutol, SM=streptomycin, R=rifampicin

**Table 4** The relationship of initial drug resistance with selected risk factors, Eastern Ethiopia, 1994/95.

| factor                 | Resistance to one or more drugs<br>pop | n(%)      | OR (95% CI)       | p (trend) |
|------------------------|----------------------------------------|-----------|-------------------|-----------|
| <b>Age (yr)</b>        |                                        |           |                   |           |
| 7-14                   | 15                                     | 5 (33.3)  | 1*                |           |
| 15-29                  | 126                                    | 38 (30.2) | 0.86 (0.25, 3.14) |           |
| 30-44                  | 92                                     | 34 (36.9) | 1.17 (0.33, 4.34) |           |
| 45+                    | 19                                     | 6 (42.3)  | 0.92 (0.17, 9.94) | *         |
| <b>Sex</b>             |                                        |           |                   |           |
| female                 | 103                                    | 30 (29.1) | 1*                |           |
| male                   | 149                                    | 52 (35.0) | 1.34 (0.75, 2.40) |           |
| <b>Address</b>         |                                        |           |                   |           |
| rural                  | 140                                    | 51 (36.4) | 1*                |           |
| urban                  | 112                                    | 31 (27.7) | 0.67 (0.37, 1.19) |           |
| <b>Residence</b>       |                                        |           |                   |           |
| out-distr.             | 146                                    | 52 (35.6) | 1*                |           |
| in-distr.              | 106                                    | 30 (28.3) | 0.71 (0.40, 1.15) |           |
| <b>HIV status</b>      |                                        |           |                   |           |
| negative               | 208                                    | 72 (34.6) | 1*                |           |
| positive               | 44                                     | 10 (22.7) | 0.54 (0.23, 1.24) |           |
| <b>Contact history</b> |                                        |           |                   |           |
| no                     | 167                                    | 52 (31.1) | 1*                |           |
| yes                    | 85                                     | 30 (35.3) | 1.21 (0.67, 2.17) |           |
| <b>Crowding</b>        |                                        |           |                   |           |
| 1-2.99                 | 114                                    | 41 (36.0) | 1.46 (0.68, 3.15) |           |
| 3-5                    | 84                                     | 26 (31.0) | 1.17 (0.51, 2.65) |           |
| >5                     | 54                                     | 15 (27.8) | 1*                |           |
| Total                  | 252                                    | 82 (32.5) |                   |           |

Note: \* = Trend was not found statistically significant ( $p = 0.56$ )

1\* = Referent category.

**Table 5** The association of acquired drug resistance with selected risk factors. Eastern Ethiopia, 1994/95.

| factor                  | Resistance to one or more drugs |           |                   | p (trend) |
|-------------------------|---------------------------------|-----------|-------------------|-----------|
|                         | pop                             | n(%)      | OR (95% CI)       |           |
| <b>Age</b>              |                                 |           |                   |           |
| 7-14                    | 3                               | 3 (100.0) | 1*                | *         |
| 15-29                   | 45                              | 20 (44.4) | 0.27 (0.01,3.29)  |           |
| 30-44                   | 31                              | 16 (51.6) | 0.36 (0.01,4.67)  |           |
| 45+                     | 7                               | 5 (71.4)  | 0.83 (0.02,25.79) |           |
| <b>Sex</b>              |                                 |           |                   |           |
| female                  | 40                              | 21 (52.5) | 1*                |           |
| male                    | 46                              | 23 (50.0) | 0.90 (0.35,2.30)  |           |
| <b>Address</b>          |                                 |           |                   |           |
| rural                   | 36                              | 21 (58.3) | 1*                |           |
| urban                   | 50                              | 23 (46.0) | 0.61 (0.23,1.59)  |           |
| <b>Residence</b>        |                                 |           |                   |           |
| out-distr.              | 53                              | 26 (49.1) | 1*                |           |
| in-distr.               | 33                              | 18 (54.5) | 1.25 (0.47,3.30)  |           |
| <b>Crowding</b>         |                                 |           |                   |           |
| 1-2.99                  | 29                              | 14 (48.3) | 1*                |           |
| 3-5                     | 37                              | 20 (54.1) | 1.26 (0.43,3.75)  |           |
| >5                      | 20                              | 10 (50.0) | 1.07 (0.29,3.91)  |           |
| <b>HIV status</b>       |                                 |           |                   |           |
| negative                | 61                              | 26 (42.6) | 1*                |           |
| positive                | 25                              | 18 (72.0) | 3.46 (1.13,10.91) |           |
| <b>Contact history</b>  |                                 |           |                   |           |
| no                      | 61                              | 31 (50.8) | 1*                |           |
| yes                     | 25                              | 13 (52.0) | 1.05 (0.37,2.94)  |           |
| <b>Treatment status</b> |                                 |           |                   |           |
| defaulter               | 51                              | 24 (47.1) | 1*                |           |
| failure                 | 21                              | 12 (57.1) | 1.50 (0.48,4.73)  |           |
| relapse                 | 14                              | 8 (57.1)  | 1.50 (0.39,5.80)  |           |
| Total                   | 86                              | 44 (51.2) |                   |           |

Note: \* = Trend was not found statistically significant ( $p = 0.49$ ).

1\* = Referent category.

## DISCUSSION

In this study the prevalence of initial resistance (32.5%) and acquired resistance (51.2%) were high. History of previous anti-tuberculosis treatment was the single most important predictor of anti-tuberculosis resistance. Acquired resistance was found to be significantly associated with drug resistance. The HIV seroprevalence among smear/culture positive cases was 20.4%.

In order to increase the validity the study and minimize sources of bias a three day training was given to the interviewers. For the interview nurses were used in the three hospitals. A closed ended questionnaire was twice pretested and used after necessary corrections were made. Supervision of both the interviewers and the laboratory technicians was made on the spot. Laboratory procedures were handled and supervised by senior laboratory technicians. A microbiologist was involved in supervising and directing the laboratory activities at the National Research Institute of Health. The potency of the sensitivity drugs was pretested and WHO guidelines were adhered throughout. All smear positive cases attending the out patient departments of the three hospitals were involved and the same reagent from the same manufacturer was used for acid fast staining.

The high prevalence of acquired resistance in this

study is in agreement with the studies done at Addis Ababa tuberculosis centre in 1978 (46%) and 1992 (46%) (40,46). The prevalence of initial resistance (32.5%) was particularly higher as compared to the previous studies done in this country which ranged between 7.5% and 15% (41-42). This may not be surprising. It is most likely because of the high defaulter rate, shortage of anti-tuberculosis drugs in the government sector, availability of anti-tuberculosis drugs in the open market which are smuggled from the neighbouring countries, unsupervised treatment and the wide practice of inappropriate prescriptions made by the private clinics in this area. War, displacement, drought, and frequent population movements with disruption of health infrastructure might have contributed to the high prevalence in this study. The fact that initial resistance has increased compared to the previous reports indicates the need to take an immediate action before the problem of drug resistance becomes a big problem. Although initial and acquired resistance to rifampicin were low (1.6%, 5.8% respectively), no rifampicin resistance was reported previously in Harar region (42). This shows that resistance to rifampicin is increasing. In addition, the high resistance to isoniazid in both new and old cases of tuberculosis and the presence of multiple drug resistance in 3.5% of old cases denotes that further delay in

implementing the introduction of short course chemotherapy with adequate supervision may endanger the control of tuberculosis (26).

Initial resistance to streptomycin is higher when compared to the previous reports (40-43). This may be due to the wide-spread abuse of streptomycin in this area. Sputum smear examinations are not routine in many of the health facilities. Therefore, patients are started on standard regimen empirically. The frequent shortages of streptomycin that were observed have led to the increased cost of streptomycin (3 Birr per 1 gram of streptomycin) in the area. A total of 360 Birr was required for finishing the two months course of streptomycin and this could not be afforded by many patients (Mitike G., Health Profile of Region 13. 1994).

Previous history of anti-tuberculosis treatment was the major risk factor for drug resistance. This agrees with several reports from different parts of the world (11,24).

This study revealed that one of five infectious cases of tuberculosis is HIV positive. Although a lower result was obtained, it is quite comparable to the report from Shashemene (southern Ethiopia) (39). It has been postulated that HIV infected pulmonary tuberculosis patients tend to be smear negative with lower bacillary load and hence are said to be less infectious (2,35).

This study adds to the growing body of evidence that HIV positive patients are equally as infectious as HIV negatives (17,18,25). WHO has estimated that one out of seven of all types of tuberculosis patients will be co-infected with HIV at the end of this century (11). In this study, this rate has already been surpassed. Thus, the HIV/TB epidemic will have a major impact on public health activities and on the health budget of Ethiopia.

Results are equivocal on the association between initial drug resistance and HIV infection in studies done in Cote d' Ivoire, Zambia and Kenya (33,47,48). However, in this study, as found in several studies in the USA (11,24,49), the overall proportion of drug resistant isolates of mycobacterium tuberculosis was found to be higher (though here not significantly so) in HIV positive patients than HIV negative patients.

Although the proportion of overall resistance showed no significant difference, acquired resistance was found to be significantly higher among HIV positive than HIV negative patients while initial resistance showed no such difference. It is a paradox that drug resistance was lower (22.7%) among those HIV positive new tuberculosis patients than HIV negative new tuberculosis patients (34.6%). On the contrary, the prevalence was higher (72.4%) among HIV positive than HIV negative (42.6%) old cases of tuberculosis. It is possible that more HIV

positive tuberculosis patients with previous history of anti-tuberculosis treatment may tend to come to the tuberculosis centre than new HIV positive tuberculosis patients who may visit other hospitals or health institutions first. This is because they are already aware of tuberculosis and would preferably go to the tuberculosis centre where they have their treatment cards. On the other hand, there are different explanations concerning drug resistance and HIV infection. It has been postulated that since most adults are exposed to *Mycobacterium tuberculosis* in developing countries, HIV induced immunosuppression may favour the reactivation of the more virulent organisms. Therefore, HIV infected patients with resistant isolates of *M. tuberculosis* may more easily progress to clinical disease than immunocompetent patients. In the USA they were able to demonstrate that HIV-infected patients with treated or cured tuberculosis might have subsequent episodes of tuberculosis either as a result of reactivation or through exogenous reinfection with resistant *mycobacterium tuberculosis* (50-53). In Kenya, it was shown that recurrence of drug resistance was higher in HIV positive patients who were put on standard regimen than short course chemotherapy which contained rifampicin. In our study no resistance was documented for the short course regimen which contained rifampicin (see

table 3). From the Kenyan study, it was also suggested that the risk of defaulting may be higher in HIV positive than HIV negative patients (48). Although not significant, HIV positive patients were more defaulters 64.3% (9/14) than HIV negative 40.5% (15/37) patients. In any case, the finding of this study suggests that an accelerating drug resistance may occur in Ethiopia due to the poor control of tuberculosis and due to the HIV epidemic. This needs to be addressed in the short term. Further longitudinal study is required to elaborate and ascertain the impact of HIV infection and on the spread of drug resistant tuberculosis in Africa, particularly in this country.

Previous studies have shown that both initial and acquired resistance can be lowered by implementing the WHO recommended tuberculosis control programme (Directly Observed Therapy) (11,17,54,55). Therefore, there is still hope to control the problem of drug resistance in this country as long as we are able to implement treatment under supervision.

*Limitations of the study:* One of the limitations of this study is that the results may not be generalizable at the national level since national drug resistance surveys require selection of health institutions by simple random sampling method. In addition, the fact that it is a hospital based study might further limit generalizability

(external validity) i.e. pulmonary tuberculosis patients who seek treatment in rural hospitals, health centres, clinics, or private clinics in the area or those who did not seek treatment were not considered. This may inflate the finding in our study since many patients with sensitive tubercle bacilli might get treatment in other health institutions. Nevertheless, the presence of this tuberculosis centre (as one of the three tuberculosis centres) for the last thirty years might have reduced the problem of generalizability since the people in the area are quite aware of the services given by this institution, and patients are drawn from all parts of the surrounding area. Therefore, it is more likely that the results are applicable in this part of the country. Above all, it will be very difficult to draw any important conclusion without involving this tuberculosis centre.

From the findings, one can say that a larger sample size may be required to detect a significant difference between HIV seropositive and HIV seronegative smear positive tuberculosis patients. Nevertheless, with the above limitations, the findings of this study will be useful for planners (involved in tuberculosis control programme), for health professionals involved in the treatment of tuberculosis patients and for those interested in further study of drug resistance and HIV infection.

## CONCLUSION

There is a high prevalence of initial and acquired anti-tuberculosis drug resistance in this hospital based study. It is likely that a similar pattern would be demonstrated in the different parts of the country where there are similar tuberculosis treatment centres. The burden on the public health services is shown by the fact that there is one HIV infected tuberculosis patient for every five infectious cases of tuberculosis; this indicates that as well as HIV negative tuberculosis patients HIV positive pulmonary tuberculosis will be an important source of infection. Apart from the poor control of tuberculosis, the HIV epidemic may enhance the spread of anti-tuberculosis drug resistance.

**RECOMMENDATIONS**

- (1) There is a need to conduct a periodic anti-tuberculosis drug resistance survey in order to assess the level and the pattern of initial drug resistance.
- (2) An alternate strategy of tuberculosis control is required such as treatment under supervision and the introduction of short course chemotherapy. The supply of anti-tuberculosis drugs and reagents should be dependable. Along with this, the availability of anti-tuberculosis drugs in the open market should be controlled.
- (3) The danger of the spread of drug resistant tuberculosis and the burden of HIV/TB epidemic should be clearly demonstrated to the political leaders, the community and the health professionals.
- (4) Treatment guidelines concerning patients infected with drug resistant strains should be prepared and distributed to the health institutions involved in the treatment of tuberculosis.

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**QUESTIONNAIRE**

INSTRUCTION: After getting a verbal consent from the patient please fill all the information needed. Collected information should be kept confidential.

Date — / — / — 87 E.C.

Name of the interviewer.....

Signature.....

**Socio-demographic**

Name of the patient.....

Code number /.../.../.../

Card number .....

1. Age /.../.../

2. Sex: (1) M (2) F

3. Address:

(1) Town/Woreda ...../.../.../

(2) Kebele/P.A/...../.../.../

(3) House number /.../.../.../.../

(4) Religion: (1) Muslim (2) Christian

(3) Others (specify).....

5. Ethnicity: (1) Oromo (2) Amhara

(3) Adere (4) Tigre

(5) Somali

(6) Others (specify).....

6. Literacy: (1) can not read or write  
(2) can read news paper  
(3) can write a letter  
(4) can read and write
7. Educational back ground: Last grade completed?  
(1) No school .  
(2) Elementary /.../.../  
(3) Secondary /.../.../  
(4) Above secondary /.../.../ +
8. Occupation: (1) farmer  
(2) government employee  
(3) merchant  
(4) student  
(5) house wife  
(6) driver  
(7) sex worker  
(6) ex-soldier  
(9) others (specify).....
9. Marital status:  
(1) married  
(2) single  
(3) widowed  
(4) divorced  
(5) Other (specify).....

10. Economic standard (Average family income per month):

- (1) < 100 Birr
- (2) 100 - 300 Birr
- (3) 301 - 500 Birr
- (4) > 500

11. Number of family members living together: /.../.../

12. Number of rooms in the housing: /.../.../

**Medical history**

13. History of previous treatment for tuberculosis?

- (1) Yes (2) No (3) Do not remember

If yes, fill questions 14 - 17

14. Type of treatment taken ?

- (1) Tablets (2) Injections (3) Both

15. Duration of treatment taken? /...../weeks

16. When did you get treatment?

- (1) /.../.../ months back
- (2) /.../.../ years ago

17. Where did you get the treatment?

- (1) TB Centre
- (2) In hospital
- (3) In a Health Centre
- (4) In a government clinic
- (5) In a private clinic
- (6) Other (specify) .....

18. Do you have other respiratory disease other than tuberculosis?

- (1) Yes            (2) No

If yes, fill questions 19 - 21

19. Type of treatment taken?

- (1) Tablets    (2) Injections  
(3) Other (specify).....

20. Duration of treatment taken? /...../ weeks

21. How did you take it?

- (1) Daily    (2) when sick  
(3) Other (specify).....

22. History of contact with a patient with cough?

- (1) None  
(2) There is history of contact with a chronic cougher  
(3) There is history of contact with a known tuberculosis patient

If the answer is 2 or 3 for the above question, fill questions 23 - 24

23. Where did you live together?

- (1) At working place    (2) same compound  
(3) same house    (4) same room    (5) same bed

24. For how long did you live together? .....months

25. depending on the above information, the patient is ?

- (1) new (2) defaulter (3) relapse (4) treatment failure (5) chronic

26. If the answer given for question number 25 is 2 i.e. if the patient is a defaulter, what are the reasons for defaulting?

- (1) I became well
- (2) Drugs were not available in the treatment centre
- (3) Drugs were not available in the private pharmacies
- (4) Could not afford to buy the drugs
- (5) I did not know that I have to come back for follow up
- (6) The drugs did not help me
- (7) The treatment centre is too far ( >10 kilometres from the village)
- (8) I could not resist the bad effects of the drugs such as vomiting, skin rash, abdominal discomfort, etc
- (9) Other.....specify.....

27. What are the sources of information for question number 25 ?

- (1) from the patient only (2) from patient card
- (3) from both

28. Do you know the duration of TB treatment ?

- (1) No
- (2) < 10 months /inadequate/
- (3) > 10 months /adequate/

Note: If the patient could not remember the type of treatment taken, try to help him or her by showing him or her a streptomycin vial and other anti-tuberculosis drugs.

Name of supervisor.....

Signature.....Date /.../.../.../

**LABORATORY REPORT***Acid Fast Staining Result*

1. Code number of the sputum /.../.../.../
2. First smear positivity grading?
  - (1) + = scanty
  - (2) ++ = moderate
  - (3) +++ = many
3. Second smear positivity?
  - (1) negative
  - (2) + = scanty
  - (3) ++ = moderate
  - (4) +++ = many

*HIV status of the patient*

4. Code number of blood sample /.../.../.../
5. First screening result? (1) positive
  - (2) indeterminate
  - (3) negative
6. Confirmatory result ? (1) positive (2) negative

*Culture and sensitivity result*

7. Code number of culture .....
8. Culture result?
  - (1) positive
  - (2) negative
9. Resistant to Isoniazid?
  - (1) Yes
  - (2) No
10. Resistant to Rifadin?
  - (1) Yes
  - (2) No

11. Resistant to Thiacetazone?

(1) Yes (2) No

12. Resistant to Ethambutol?

(1) Yes (2) No

13. Resistant to Streptomycin?

(1) Yes (2) No

Name of Laboratory technician.....

Signature.....

Date of report /.../.../.../

Name of supervisor.....

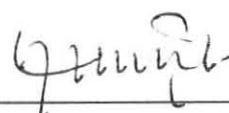
Signature.....

Date /.../.../.../

# DECLARATION

I, the undersigned, declare that this is my original work and has not been presented for a degree in this or any other university and that all sources of material used for this thesis have been duly acknowledged.

Name GETNET MITIKE

Sign 

Place ADDIS ABABA

Date of submission MAY, 1995