*Original Article*

# A study on Prevalence of Drug Resistance in Drug Default Pulmonary Tuberculosis

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**Abstract:**

**Background:** The emergence of resistance to drugs used to treat tuberculosis (TB), and particularly multidrug-resistant TB (MDR-TB), has become a significant public health problem in a number of countries and an obstacle to effective global TB control.

**Method:** This is a prospective randomized cross sectional study to estimate the magnitude of MDR tuberculosis in two hospitals in Khartoum, Sudan. 111 patients who had defaulted their tuberculosis treatment on previous occasions and had presented to the hospital with several symptoms were studied. All patients provided sputum, which was examined for the presence of acid fast bacilli (AFB) by Ziehl- Neelsen stain. Sputa were also sent to the reference laboratory for mycobacterial culture and drug susceptibility testing. All culture positive sputa had drug sensitivity tested to the first line anti-TB drugs used in Sudan namely Streptomycin, Isoniazid, Rifampicin and Ethambutol.

**Results:** Out of the 111 patients, 29.7% (n=33) were AFB sputum smear positive and 40.5% (n=45) were sputum culture positive for mycobacterium.

Sensitivity testing revealed that 48.9% (n=22) were resistant to Streptomycin, 62.2% (n=28) were resistant to Isoniazid, 55.6% (n=25) were resistant to Rifampicin and 37.8% (n=17) were resistant to Ethambutol. 42% ( n=19) of the patients were resistant to Rifampicin and Isoniazid only, while 26.6% (n=12) were resistant to all the first line drugs (Streptomycin, Isoniazid, Rifampicin and Ethambutol).

**Conclusion:** This study showed that the prevalence of MDR tuberculosis among the defaulters in Khartoum is much higher than what was reported previously. This study highlights the extent of the problem of drug resistance in Khartoum and emphasises the need for proper treatment and strengthening of the short course direct observed therapy strategy.

**Keywords:** Streptomycin, Isoniazid, Rifampicin and Ethambutol.

Africa, home to 11% of the world's population, carries 29% of the global burden of tuberculosis cases and 34% of TB-related deaths, and the challenges of controlling the disease in the region have never been greater with the emergence of HIV infection[1]. In sub-Saharan Africa HIV/AIDS is dramatically fuelling the spread of TB. This disease is a major cause of death among people living with HIV. MDR-TB and XDR-TB (extensive multidrug resistant tuberculosis defined as resistance to at least rifampicin, isoniazid, a second line injectable drug capreomycin, kanamycin or amikacin and a fluoroquinolone) are highly lethal in people living with HIV. Studies have shown case fatality rates of over 90%[1]. Drug-resistant TB is therefore a major threat to the effectiveness of both TB treatment and anti-retroviral treatment programs.

Sudan alone carries 8-11% of the TB burden in the Eastern Mediterranean Region. In the year 2006, the estimated incidence of new smear-positive cases was 101 per 100,000 populations, which gave a total estimation of 36,741 new smear-positive cases. In addition, it has been estimated that the prevalence of all TB forms was to be 400 cases per 100,000 populations (145,021

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prevalent cases). The overall estimated death rate including HIV infected TB cases was 65 per 100,000 population in 2005[2]. In the year 1999, a case notification of (26,950) had been acheived. But since then, the notification curve showed a gradually declining plateau. The year 2005, witnessed the highest case notification (27,562). The estimated number of smear positive cases in 2007 was 26,922 cases of which only 9,836 were notified to the national tuberculosis control programme[3]. This means that the case detection rate is 36.5%, which is far beyond the target of 70%, which can be attributed to civil war in Darfur and confilict in the east part of the country.

With regards to the situation of MDR-TB in the Sudan, no national survey has been carried out to determine the magnitude of MDR-TB. However, the prevalence of MDR-TB in new smear-positive TB was estimated to be 10.1%[2]. This estimated prevalence was based on observations from case notification (1993-2004) and treatment outcomes (1995-2003); the average percentage of all re-treatment cases was 6.7% of notified cases and the average failure rate was 2.7% in all treated new smear-positive cases. This figure is believed to be an overestimation that necessitates a need for more accurate and realistic estimation[2].

In the present study we looked at the prevalence of MDR tuberculosis among defaulters attending two chest hospitals in Khartoum, Sudan.

**Methods:**

This is a random cross sectional study done at Elshaab and Abuange hospitals (tertiary hospitals) in Khartoum, Sudan. The majority of the patients in this study were from Khartoum state and few from central Sudan, Kordofan, Darfur and South Sudan. Extrapulmonary and new pulmonary tuberculosis patients were excluded from the study.

A random selection of 111 patients who had defaulted their antituberculosis treatment on previous occasions and had presented this time in these hospitals because of various symptoms like cough, fever, haemoptysis and night sweats were included. This study was carried out over a period of one year from January 2007 to December 2007. All these patients were investigated with sputum examination for AFB (acid fast bacilli) smear by Ziehl- Neelson staining technique and culture for mycobacterium. Culture was done on Lowenstein Jensen media and the culture positive samples subjected to sensitivity testing for first line anti-tuberculus drugs Rifampicin, Isoniazid, Streptomycin and Ethambutol. Data from patients were collected using anonymous questionnaire.

**Results:**

A random of 111 patients coming from different localities and presenting with different symptoms were enrolled (Table1).

Table 1 Patient characteristics

| Characteristics | | N (%) |
|---|---|---|
| Age (years) | Median | 39 |
| Sex | Male | 83(74.8) |
| | Female | 28(25.2) |
| Presentation | Cough | 111(100) |
| | Fever | 93(84) |
| | Haemoptysis | 31(28) |
| | Night sweats | 87(78) |
| Residence | Khartoum | 75(67.5) |
| | Central | 23(20.7) |
| | Darfour | 2(1.8) |
| | Algadrif | 6(5.4) |
| | South | 1(0.9) |
| | Kordofan | 4(3.6) |
| Prev. treatment* | Once | 91(82) |
| | Twice | 17(15.3) |
| | Thrice | 3(2.7) |

* Previous treatment.

Out of these patients, 29.7% (n=33) were AFB sputum smear positive and 40.5% (n=45) were sputum culture positive for mycobacterium (Table2).

Table2. Sputum results ( n = 111)

| | Result | No (%) |
|---|---|---|
| AFB smear | Positive | 33 (29.7) |
| | Negative | 78 (70.3) |
| Culture for Myco.* | Positive | 45 (40.5) |
| | Negative | 66 (59.5) |

* Mycobacterium Tuberculosis.

Sensitivity testing revealed that 48.9% (n=22) were resistant to Streptomycin, 62.2% (n=28) were resistant to Isoniazid, 55.6% (n=25) were resistant to Rifampicin and 37.8% (n=17) were resistant to Ethambutol (table3).

Table 3 Resistance to anti-tuberculosis drugs (n=45)

| DST | N (%) |
|---|---|
| Streptomycin | 22 (48.9) |
| Isoniazid | 28 (62.2) |
| Rifampicin | 25 (55.6) |
| Ethambutol | 17 (37.8) |

42% ( n=19) of the patients were resistant to Rifampicin and Isoniazid only, while 26.6% (n=12) were resistant to all the first line drugs (Streptomycin, Isoniazid, Rifampicin and Ethambutol).
Out of the 12 patients who were resistant to all four drugs 33.3% (n=4) had defaulted their treatment in the initial phase and the majority, 66.6% (n=8) had defaulted in the continuation phase.
Moreover, 33.3% (n=4) had received treatment under category one while 66.6% (n=8) had been treated under category two. (Multidrug Resistant Tuberculosis). Of these 19 patients, 31.5% (n=6) had defaulted in the intensive phase and 68.5% (n=13) had defaulted in the continuation phase, also 19 patients, 21% (n=4) had been treated under category one and 79% (n=15) had been treated under category two.

**Discussion:**

This study showed that the prevalence of MDR tuberculosis among the defaulters in Khartoum is much higher than what was reported previously[4]. This study highlights the extent of the problem of drug resistance in Khartoum and emphasises the need for proper treatment and strengthening of the short course direct observed therapy strategy.

The Stop TB Strategy launched in 2005 by WHO is based upon building on and enhancing directly observed treatment short course (DOTS) and identifies the management of MDR-TB as a priority[5]. The strategy recognizes the need to provide care to all patients affected by TB, whether the disease is caused by drug susceptible or drug-resistant bacilli. Therefore, the management of MDR-TB now needs to be integrated into comprehensive national TB control plans in order to comply with the new Stop TB Strategy.
Due to paucity of data from Africa, the WHO found it difficult to accurately estimate the true burden and trends of MDR-TB and XDR-TB in this region. The current study highlighted the need for more robust data to assess the extent of the multi-drug resistant tuberculosis in the region.

However, the WHO seems to have accepted general estimates of resistance, in previously treated patients, in Africa to be in the order of 10% for Streptomycin, 18% for Isoniazid, 7.5% for Rifampicin and 4% for Ethambutol. In contrast, globally the prevalence of resistance for Streptomycin is 20.5%, Isoniazid 28%, Rifampicin 18% and Ethambutol 11%[3]. Furthermore, data on previously treated cases were available for 66 countries[6]. Resistance to at least one anti-TB drug (any resistance) ranged from 0% in three European countries to 85.9% in Tashkent, Uzbekistan.

The highest level of drug resistance was recorded in Baku, the capital of Azerbaijan, where nearly a quarter of all new TB cases (22.3%) were reported as multidrug-resistant. Proportions of MDR-TB among new TB cases were 19.4% in Moldova, 16% in Donetsk in Ukraine, 15% in Tomsk Oblast in the Russian Federation and 14.8% in Tashkent in Uzbekistan. There are very little

data from Africa, the region of one of the highest prevalence of tuberculosis in the world due to lack of equipment and trained personnel to identify drug resistant tuberculosis. It is therefore difficult to estimate accurately the true burden of multidrug resistant tuberculosis in this region. In Africa it is estimated that 2.2 percent of the newly diagnosed and 9.2% in previously treated tuberculosis cases are MDR tuberculosis which is among the lowest in the world[6].

In this study resistance to streptomycin is the highest followed by isoniazide and the lowest resistance seems to be to ethambutol. Although the majority of defaulters were in the continuation phase at least one third defaulted in the intensive phase and this may well be related to injectable streptomycin in the initiation phase. Since streptomycin is associated with the highest resistance rate it is reasonable to suggest that it should be replaced by ethambutol in the intensive phase and it should be reserved as a second line treatment.

The present study, however, showed a much higher resistance level to these drugs than expected[4]. This may partly be due to biased data collection in patients who re-presented to hospital because of recurrence of their symptoms.

The study sample has been a random selection of a small number and a larger study group would have been more reliable. Moreover there are no data on the exact number of tuberculosis patients registered with these centers and so we do not know the exact magnitude of tuberculosis. In this study we have not considered the HIV status of the patients. However, Sudan has not got a high HIV prevalence as compared to other African countries and so the prevalence of MDR TB will be much higher in those countries[7, 8]. Also there is no information about primary resistance.

Treatment of MDR-TB should be at a specialized centre with standard microbiology laboratory facilities. Though treatment guidelines including standardized, empirical and individualized approaches have been laid down by the WHO but therapy should be tailored to the needs of the particular patient. Treatment of MDR-TB is difficult, complicated, much costlier, challenging and needs experience and skills. 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. Current proposal of DOTS Plus by WHO highlights the comprehensive management strategy to control MDR-TB. MDR-TB is a man-made problem and its emergence can be prevented by prompt diagnosis and effective treatment of all TB cases. Adoption of DOTS to prevent the resistant/multi-drug resistant strains and careful introduction of second line drugs to treat patients with MDR-TB are the top priorities for the proper control of MDR-TB[7, 9].

To forestall disastrous consequences, infection control, rapid case detection, effective treatment, and expanded program capacity are needed urgently[9]. MDR-TB is an emerging and difficult public health problem worldwide. In the presence of resistance to key first-line antituberculous agents, treatment with less effective and more toxic second-line agents must be instituted. Consequently, patients remain infectious for a longer period and require prolonged courses of treatment. There may be a role for surgery in selected cases. Care must be taken in terms of isolation procedure and infection control in MDR-TB and such facilities are yet to be available in Sudan. Although the diagnosis is made microbiologically, there are certain factors that predispose to the emergence of MDR-TB, notably a history of previous treatment for TB, particularly if that treatment was inadequate or incomplete as has been highlighted by this study. Prescription errors made by physicians also contribute, such as adding a single drug to a failing anti-TB regimen. Data on the extent and magnitude of these practices are not available. The use of

DNA amplification techniques, for example polymerase chain reaction has resulted in the rapid diagnosis of MDR-TB compared with traditional solid culture media. These techniques are yet to be available in Sudan.

Treatment of MDR-TB usually involves five drugs to which microbiologically, the organism has been shown to demonstrate susceptibility, and one of these drugs should be an injectable agent. Within Sudan National TB Program there seems to be a provision for this high cost treatment. However, there is a need for greater research into developing more effective antituberculous medications and immunotherapy may play an adjunctive role in future management[10, 11].

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