

East African Medical Journal Vol. 79 No. 1 January 2002

TUBERCULOSIS RE-TREATMENT OUTCOMES WITHIN THE PUBLIC SERVICE IN NAIROBI, KENYA

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TUBERCULOSIS RE-TREATMENT OUTCOMES WITHIN THE PUBLIC SERVICE IN NAIROBI, KENYA

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ABSTRACT

Objectives: This study was undertaken to describe treatment outcomes in patients started on a re-treatment drug regimen, assess the quality of follow up procedures and the adequacy of the currently advocated re-treatment drug regimen in Nairobi, Kenya.

Design: A retrospective study.

Setting: Mbagathi District Hospital (MDH), Nairobi, a public hospital that serves as the Tuberculosis (Tb) referral centre for Nairobi

Materials and methods: The Tb register at the MDH was used to identify patients who were on the re-treatment regimen for Tb. Case records for these patients were then retrieved. From these sources, information on age, sex, HIV status, previous and current tuberculosis disease and drug regimens, adherence to treatment and treatment outcomes, was obtained. Descriptive statistics was used to analyse the data.

Results: Of the total of 4702 patients registered at the MDH between 1996 and 1997, 593 (12.6%) were patients with either recurrent Tb, returning to treatment after default or had failed initial treatment. Of the 593 patients, case records were unavailable for 168 and 17 were children below the age of ten in whom the diagnosis of Tb was uncertain making a total of 185 patients who were excluded from the study. Of the remaining 408 patients, 77 (18.9%) were cured, 61 (15.0%) completed treatment without confirmation of cure, two (0.5%) defaulted, six (1.5%) died and 262 (64.2%) had no outcome information. There were no treatment failures. Treatment success defined as cure or treatment completion was achieved in 94.5% of the 146 patients in whom outcome data were available. HIV positive patients had a statistically significant poorer success rate (34/40, 85%) when compared with HIV negative patients (104/106, 94%), $p=0.004$. *Mycobacterium tuberculosis* culture and drug susceptibility testing, was not done.

Conclusion: The high number of patients with no treatment outcome information at the MDH is worrying, as these patients may harbour drug resistant bacilli and reflects an inadequate follow up service for Tb re-treatment in Nairobi. However, where treatment outcomes could be assessed, the currently advocated re-treatment regimen achieved a high success rate. These observations point to an urgent need to improve Tb documentation and follow up procedures within the public service in Nairobi in order to forestall the emergence and spread of drug resistant Tb.

INTRODUCTION

Kenya has a huge and rising tuberculosis (Tb) disease burden and has recently been included in the list of the top 22 countries with the highest Tb disease burden in the world(1). The Tb case notification rate has more than tripled from 51 per 100,000 population in 1987 to 201 per 100,000 population in 1999(2). The major reason for this increase is the pandemic that has been occasioned by infection with Human Immunodeficiency Virus (HIV). HIV is known to be the most potent risk factor for the reactivation of latent Tb and may also lead to rapid

progression of new infection to disease(3). Thus, the virus has been roundly blamed for the unprecedented high Tb disease incidence that has been witnessed in sub-Saharan Africa in recent years(4-6). However, other factors may be contributing to the poor Tb situation in Africa, Kenya included. Principle among these factors is the rising poverty and consequent social deprivation. Poverty and Tb are known to be closely associated. It has been shown that Tb rates in the industrialised world fell long before the introduction of specific chemotherapy and BCG vaccination, a phenomenon that has been attributed to improved social conditions and possibly the natural history

of the pandemic(7). It has also been shown that a strong relationship between Tb and social deprivation exists in several cities in the UK(8,9).

The Directly Observed Therapy Short course (DOTS) strategy as advocated by the World Health Organisation (WHO) and International Union Against Tuberculosis and Lung Disease (IUATLD)(10) has been universally adopted for the control of Tb in Kenya since 1994. However, DOTS is not strictly enforced and especially after the withdrawal of streptomycin for the treatment of new Tb, patients self supervise treatment except when they are hospitalised. When streptomycin was used for the treatment of all smear positive pulmonary tuberculosis (PTB) in the intensive phase, patients would report daily for a streptomycin (S) injection and simultaneously receive an appropriate dose of a fixed dose combination formulation of Rifampicin(R), Isoniazid (H) and Pyrazinamide (Z).

For patients who have previously been exposed to anti-tuberculosis drugs including those with recurrent Tb, those returning to treatment after default and those who have failed initial treatment, the WHO/IUATLD recommended re-treatment regimen, consisting of two months, of S, R, Z, H and Ethambutol (E) followed by a month HRZE and five months of HRE (2SRHZE/HRZE/5HRE)(10) is used in Kenya. This re-treatment drug regimen is not restricted to those with smear positive pulmonary disease but is used also for smear negative suspected pulmonary disease as well as extra-pulmonary Tb (EPTB). In Nairobi, all patients requiring or suspected to need this form of treatment are referred to the Mbagathi District Hospital (MDH), a public health facility that has for a long time been used as the national Tb referral centre. At this hospital, patients are evaluated, registered and started on treatment. Patients may then be referred back to peripheral health units to continue treatment but are instructed to report back to the specialised Tb clinic at the MDH for follow up and assessment of treatment outcome. Since patients on re-treatment represent a pool of individuals who may harbour drug resistant bacilli, this retrospective study was carried to evaluate the efficiency of the follow up procedures, treatment outcomes and the adequacy of the currently advocated re-treatment regimen in the public sector within Nairobi.

MATERIALS AND METHODS

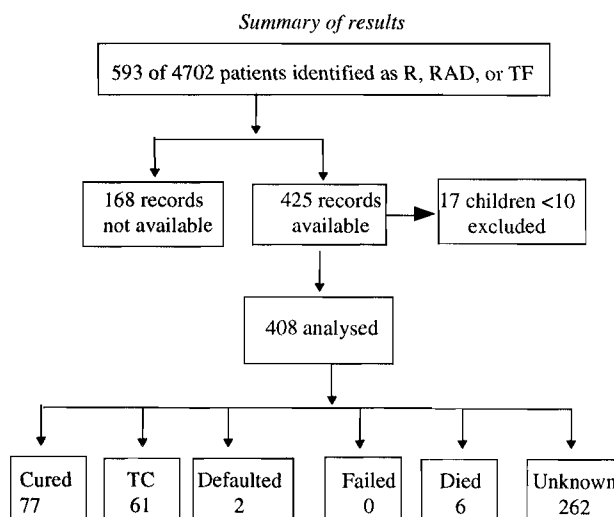
The MDH, formerly the Infectious Diseases Hospital, in Nairobi is a public hospital with a capacity of 169 beds that has been offering Tb services since its inception in 1956. The hospital served as the Tb treatment center for Nairobi offering in and out-patient services and also as the referral center for difficult cases of Tb from all over the country until 1995 when it was converted to a general medical and paediatric hospital. Despite the change of status, the hospital has continued to serve as the Tb referral center especially for Nairobi. Patients referred to this hospital for re-treatment include: (i) patients who have failed initial treatment defined as smear positivity by the fifth month of treatment when on a short course regimen; (ii) patients returning to treatment after a period of default in excess of one or more months and; (iii) patients with recurrent Tb after successful

initial treatment. From the Tb register at the hospital we identified all such patients registered in 1996 and 1997. The Tb register in this hospital also serves as the treatment register and thus treatment outcomes should have been entered in the register. However, the outcome data is often not entered in the register. We therefore retrieved the case records of all identified patients in an attempt to obtain information that was not available from the register. From both the registers and the case records we sought the following information: age, sex, HIV status, type of previous and new Tb plus drug regimens used, adherence to treatment and treatment outcome. The data obtained was entered into the computer using a Dbase4 computer package and analyzed using SAS statistical package. As a result of missing data we were only able to do descriptive analysis.

RESULTS

Of the 4702 Tb patients registered at the hospital between 1996 and 1997, 593 (12.6%) required re-treatment. Of these 402 (67.8%) patients had recurrent Tb, 177 (29.8%) were returning to treatment after default and 14 (2.4%) had failed initial treatment. Case records were unavailable for 168 patients and 17 were children under the age of 10 in whom the diagnosis of Tb was uncertain. The results presented are therefore for the remaining 408 patients (Figure 1).

Figure 1



The mean age was 32.1 (± 10.1) years with a median of 32.0 years and a range of 16-82 years. There were 283 males with a male to female ratio of 2.3: 1.

The type of previous Tb disease in the 408 patients is shown in Table 1. Of the 408 patients, 377 (92.4%) had pulmonary tuberculosis (PTB). Of these 175 (42.9%) were smear positive, 38 (9.3%) were smear negative disease while the smear status was unknown in 164 (40.2%). Of the 31 patients who previously had EPTB, pleural disease was the most common form seen in 16 (51.6%) patients. Of the 408 patients, 232 (56.9%) had previously been treated with a 12-month drug regimen

(1SHE/11HE), 48 (11.8%) with a short course drug regimen, 33 (8.1%) with a non-programme regimen while in 95 (23.3%) patients, the regimen used was unclear. Clinical case records indicated full adherence to prescribed treatment in 190 (46.6%) of the 408 patients while 128 (31.3%) were non-adherent and in 90 (22.0%) patients adherence information was not available.

Table 1

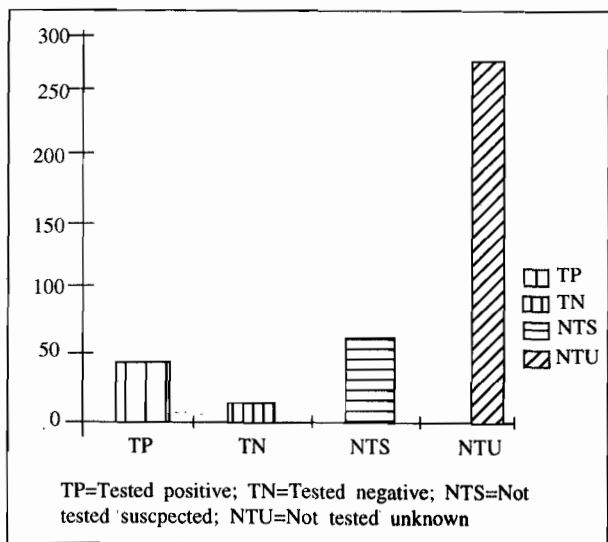
Type of previous and new Tb disease in patients on re-treatment at MDH, 1996-1997

	Previous Tb No (%)	New Tb No (%)
Smear positive PTB	175 (43.0)	301 (74.0)
Smear negative PTB	38 (9.3)	49 (12.0)
PTB smear unknown	164 (40.3)	33 (8.1)
Pleural Tb	16 (3.9)	4 (1.0)
Nodal Tb	5 (1.2)	5 (1.2)
Miliary Tb	2 (0.5)	10 (2.5)
Tb meningitis	3 (0.7)	4 (1.0)
Pericardial Tb	2 (0.5)	0 (0.0)
Other	2 (0.5)	1 (0.2)
Total	407	407

The type of new Tb disease is shown in Table 1. PTB was the most common type of disease seen in 383 (93.8%) of the 408 patients. Of these, 301 (78.6%) were smear positive, 49 (12.7%) were smear negative disease while the smear result was not recorded in 33 (8.6%) patients. EPTB was seen in 25 (6.2%) of the 408 patients. Of these miliary Tb was the most common type seen in 10 (40%) patients followed by nodal disease in 5 (20%) patients while pleural and meningeal disease was seen in 4 (16%) patients each.

Figure 2

HIV status of Tb patients on re-treatment at MDH, 1996-1997



The HIV serostatus of the 408 patients is shown in Figure 2. Only 46 (11.2%) patients were tested for HIV. Of

these 38 (82.6%) tested positive and eight (17.3%) tested negative. Although there was no evidence to indicate that a HIV test had been carried out, in 82 (20%) of the 408 there were clinical conditions including Herpes zoster, Kaposi sarcoma, oropharyngeal candidiasis and recurrent or persistent diarrhea that were suggestive of HIV infection. Assuming that all the 38 patients who tested positive plus the 82 who were strongly suspected to be positive were HIV infected (n=120) and that the 8 patients who tested negative plus the 280 patients with no obvious evidence of HIV infection were negative (n=288), the HIV prevalence in this group of patients would be 29.4% (120/408).

The WHO/IUATLD advocated re-treatment drug regimen was used in 370 of the 408 (90.7%) patients. In 38 (9.3%) patients other regimens were used, the most common of which was the regimen used for new smear positive pulmonary Tb (2SRHZ/6HE). Using clinic attendance as a surrogate marker of adherence to treatment, 112 (27.5%) of the 408 patients were presumed to have been fully adherent to treatment while 11 (2.6%) were non-adherent. In 285 (69.9%) of the 408 patients the case records had no reliable follow up information and therefore adherence status could not be ascertained.

Table 2

Outcome of Tb re-treatment at MDH, 1996-1997

Outcome	No (%)
Cured	77 (18.9)
Completed treatment (No smear)	61 (15.0)
Defaulted	2 (0.5)
Failed treatment	0 (0)
Died	6 (1.5)
No information (includes transfers)	262 (64.2)

The outcome of re-treatment is shown in Table 2. Outcome data was only available in the 146 (35.8%) of the 408 patients. Of these 77 (52.7%) had a negative sputum smear result towards the end of treatment and were therefore classified as cured, 61 (41.7%) completed treatment but no smear was done at the end of treatment, two (1.3%) defaulted from treatment and six (4.1%) died. Thus, successful treatment defined as cure or treatment completion was achieved in 138 of 146 (94.5%) patients who had an outcome data available. In 262 (64.2%) of 408, the treatment outcome could not be assessed from the records available at the MDH. Some of these patients had been transferred out to other districts but the majority were treated in peripheral treatment centers in Nairobi and should have been followed up at the specialised clinic in this hospital. When outcome was assessed in relation to HIV status, a successful outcome was obtained in 104 (98.1%) of 106 HIV negative patients against 34 (85%) of 40 of HIV positive individuals. This difference was statistically significant with a p-value of 0.004. However, the HIV status was confirmed in only 46 (11.2%) of the 408 patients studied.

DISCUSSION

With decentralisation of Tb services in Nairobi, the Kenyan capital, sputum smear microscopy is available in virtually all the city's health centres and the two public hospitals. When Tb is diagnosed in the health centres the patient is referred to one of three Tb registration centres in the city namely MDH, Ngaira Avenue Chest Clinic and the Kenyatta National Hospital. After registration the patient is either referred back to one of the city's health centres or is retained at the registration centre, which then becomes the patient's treatment point. As mentioned previously all patients requiring re-treatment in accordance with Tb control programme guidelines are registered at the MDH. These patients may then be referred to any of the city's health centers to receive the prescribed treatment but are instructed to report to the specialised clinic at MDH from time to time for follow up and assessment of outcome. Our study demonstrates clearly that this patient follow up procedure does not work very well. Thus, 64.2 % of the patients we studied did not come back to the clinic at the MDH for follow up and assessment of treatment response. This represents inadequate follow up in the city, of patients who potentially may be harbouring drug resistant bacilli. It is possible that some of these patients escaped treatment altogether and may have served as sources of transmission of potentially drug resistant bacilli.

It is common knowledge that previous exposure to anti-tuberculous drugs is the strongest risk factor for drug resistance(11). In the recent WHO coordinated global anti-Tb drug resistance surveillance acquired drug resistance to any drug was found to be a median of 36.0% in re-treatment cases compared to a median of 9.9% in new patients(12). The current WHO/IUATLD advocated re-treatment drug regimen was designed to overcome resistance to H and/or E and/or S(13). However, in the presence of multi-drug resistant Tb, defined as the combined resistance to Isoniazid and Rifampicin this regimens often fail as was demonstrated by Kimmerling *et al*(14) in Tb patients from the prison system in Siberia where success rates of only 35% were obtained. It is therefore reassuring to note that where outcomes could be assessed, a high success rate of 94.4% prevailed in our study using this regimen. This suggests a low prevalence of acquired resistance to both R and H in these patients and indicates that the currently advocated re-treatment regimen is adequate in our setting. It is imperative to note that routine culture and drug susceptibility assays of *Mycobacterium tuberculosis* (*M. Tb*) isolates are not available within the public Tb service in Kenya. We are therefore unable to report the drug susceptibility patterns of the bacilli that our study patients were infected with. A study from Ethiopia that examined the pattern of anti-Tb drug resistance in patients on re-treatment found very high rates of resistance to first line anti-Tb drugs(15). In that study resistance to H, S, R and E was 44%, 28%, 12% and 2% respectively. Even more worrying was the high resistance to second line, less commonly used, drugs like

cycloserine and ethionamide. In Kenya the obvious consequence of this incapacity is that patients with drug resistant Tb may escape detection thus creating a pool for the transmission and spread of lethal bacilli unhindered for a long time. Fortunately for Kenya several studies that have examined the prevalence of drug resistant *M. Tb* have demonstrated a low prevalence of resistance to most drugs except for isoniazid where rates of resistance of up to 10% have been found(16-18). This is of course no reason for complacency and efforts at periodic monitoring and evaluation need to be emphasised. While it can be argued that routine culture and drug susceptibility assays for *M. Tb* for all patients cannot be afforded in a resource poor country like Kenya, there is merit to institute this at programme level for patients with recurrent Tb or those who have failed initial therapy and those who are returning to treatment after default. This is the only way that the problem of drug resistance can be detected early and remedial measures instituted.

The calculated HIV sero-prevalence of 29.4% in this group of patients is lower than that obtained in a survey conducted by the National Leprosy and Tuberculosis Control Programme (NLTP) in 1994(19). In that study the HIV sero-prevalence in new patients with all forms of Tb in Nairobi was found to be 36%. The weighted national average was 40% but ranged from 18% in Trans Nzoia in the Rift valley province to 78% in Siaya in western Kenya. The calculated HIV sero-prevalence rate of 29.4% in our study patients is therefore likely to be a gross underestimate, but it signifies the lack of routine HIV counselling and testing in Tb patients in Nairobi and the rest of Kenya. Only 46 of the 408 patients studied were tested for HIV. Additionally case notes are not immaculately maintained and some of the patients assumed to be negative may have had HIV related conditions that were not recorded in the case notes. With the continued rise in the incidence of both HIV and Tb in Kenya the number of patients with recurrent Tb may be expected to increase in the future. HIV infected individuals have been shown to have a markedly increased risk of recurrent Tb that may primarily be due to re-infection in a high endemic area like Kenya but could also be due to true relapses(20-22). If reinfection is the primary mechanism for recurrent Tb and if it is shown that *M. Tb* isolates from such patients are sensitive to standard regimens it may be prudent to treat these patients in the same manner as new patients with significant cost savings. The WHO/IUATLD recommended re-treatment drug regimen is the most expensive of the regimens used for non-MDR-Tb(23). The cost savings in such an approach has to be balanced against the potential hazards of facilitated transmission of drug resistant bacilli as a result of treatment failures. Our results indicate a poorer prognosis of those patients that are dually infected with HIV-Tb and emphasise the difficulties that high HIV prevalence countries may have in attempting to achieve the WHO target of curing 85% of detected Tb patients(9).

The lack of re-treatment outcome data for 64.2% of the patients we studied is worrying. With decentralisation

of the Tb service and a non-existent patient tracking system it is easy for patients to be lost to follow up. It is not easy to ascertain that patients actually report to their assigned treatment centres in the absence of a system, which enables these treatment centres to "communicate with each other". A major limitation of our study, in addition to that of missing data as a result of the retrospective nature of the study, is that we were unable to inspect Tb treatment registers in the city's health centres for logistical reasons. We are therefore unable to report on the proportion of patients referred to the health centres who actually did receive treatment at these health units. Our results should therefore be interpreted with caution. However the study results highlight the need to develop and implement a workable patient documentation and tracking system that minimises the number of patients who get lost from the Tb service. This is crucial especially for patients who may be carrying drug resistant M. Tb strains.

In conclusion we have shown that there is inadequate follow up of Tb patients who potentially may harbour drug resistant Tb in Nairobi. However, the currently advocated retreatment regimen appears to be adequate and affords a high success rate in both HIV negative and positive patients. Follow up procedures and patient tracking systems need to be improved and strengthened otherwise the city may not even know when it has been hit by an epidemic of drug resistant Tb.

ACKNOWLEDGEMENTS

This work was financed by the National Leprosy and Tuberculosis Control Programme (NLTP). We would like to thank the staff at the Tb clinic, MDH, for their assistance in retrieving the case records, Ms. Judy Rauga Gichu for the data entry work and The Director, KEMRI for permission to publish this paper.

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