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Five year review of treatment outcome of Directly Observed Therapy (DOT) for re-treatment pulmonary tuberculosis patients in UCH, Ibadan, Nigeria

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Summary

Tuberculosis (TB) is a major health problem in Nigeria. The country is currently fourth among the 22 high-burden countries (HBCs) of the world, with an incident of all new cases of 311/100,000 population per year out of which 137/100,000 population are smear positive and prevalence of 616/100,000 population. To highlight the burden of re-treatment smear positive pulmonary TB with and without HIV infection and determine how Directly Observed Therapy (DOT) using the re-treatment regimen has affected the treatment outcome in the management of these patients. A Five-year retrospective study from April 2003 to March 2008 to evaluate the treatment outcome data of re-treatment pulmonary TB who were also screened and confirmed for HIV at the outpatient clinic of the University College Hospital Ibadan, Nigeria. The effect of HIV status and treatment outcome was assessed so also the prevalence of HIV among recurrent PTB patients. The total number of cases assessed was 127. Majority of the patients were between the ages of 20 to 49(73.2%). Forty-two of the PTB patients were HIV positive (33.1%). The treatment outcome was as follows: Cured 81(63.8); Treatment completed 13(10.2%); Died 22(17.3%); Defaulted four (3.1%) and transferred out seven (5.5%) More patients were cured and had treatment completion among the HIV negative patients compared with HIV positive patients ($p<0.0001$) The mortality was higher in those with HIV positive than negative patients ($p <0.0001$). Re-treatment pulmonary TB is frequent at this referral centre. A contribution to re-treatment prevention entails more rigorous management of new TB cases, particularly at lower levels of care. This effort will reduce the emergence of multi-drug resistant (MDR-TB) tuberculosis

Keywords: *Tuberculosis; pulmonary; re-treatment; HIV prevalence and clinical outcome*

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Résumé

La tuberculose est un problème de santé majeur au Nigeria. Le pays est actuellement le quatrième parmi les 22 pays les plus attaques dans le monde, avec un incident de tout les nouveaux cas de 311/ 100 000 population par an desquels 137/100 000 population sont détectés positif et la prévalence de 616/100 000 population. Pour illuminer la souffrance des cas d'échecs des la tuberculose pulmonaire ayant les lames positives avec ou sans infection du VIH et déterminer comment une thérapie directement observée utilisant le régiment de retraitement avait affecte le résultat du traitement dans le management de ces patients. Une étude rétrospective de 5 ans (de Avril 2003 à Mars 2008) pour évaluer les données des résultats du retraitement pulmonaire de tuberculose qui était aussi testés et confirmés séropositifs au Collège Hospitalier Universitaire Ibadan, Nigeria. L'effet du status sérologique et les résultats des traitements étaient déterminé, ainsi que la prévalence du VIH parmi les Patients Tuberculeux récurrents. Le nombre total des cas étudié était de 127. la majorité des patients était âgée de 20 à 49 (73.2%). Quarante deux des PTB était séropositifs (33.1%). Les résultats des traitements étaient tel qu'il suit: guéris 81 (63.8%); traitement complet 13 (10.2%); décédés 22 (17.3%); défectueux quatre (3.1%) et transférés ailleurs sept (5.5%). La plupart des patients était guéris et recevait des traitements complémentaires parmi les patients séronégatifs comparé aux patients séropositifs ($p<,0.0001$). Le taux de mortalité était plus élevé chez les patients séropositifs que chez ceux séronégatifs ($p<0.0001$). Le retraitement de la tuberculose pulmonaire est fréquent dans ce centre de référence. La contribution du retraitement de prévention demande un management plus rigoureux des nouveaux cas de TB, particulièrement à un niveau bas des soins. Cet effort va réduire l'émergence des souches résistantes a plusieurs antituberculeux.

Introduction

It is known that the global burden of tuberculosis (TB) is increasing in developing countries of Africa and Asia where about two- third of the cases reside [1].

According to current World Health Organization (WHO), TB is a major public health issue in Nigeria [2]. Currently, the country ranks fourth among the 22 high-burden Countries (HBCs) of the world, with an incidence of all new cases of TB of 311/100,000 population per year out of which 137/100,000 population are smear positive and prevalence of 616/ 100,000 population [3]. The mortality rate is 81 cases per 100,000 populations [2]. Nigeria has the second highest burden in Africa [2]

Tuberculosis (TB) and the Human Immunodeficiency Virus (HIV) are among the 10 leading causes of death in Nigeria and indeed Africa [3,4]. TB is responsible for about 30% of deaths among the People Living With HIV/AIDS (PLWHA) [3].

The National Tuberculosis and Leprosy Control Programme (NTBLCP) of the Federal Ministry of Health, Abuja was established in 1988 [4]. The goal of the National TB program is to reduce the burden of TB by 2015 in line with the Millennium Development Goals (MDGs) and the STOP TB Partnership targets [4]. Some of the targets are to detect at least 70% of the estimated infectious (smear-positive) cases and to achieve a cure rate of at least 85% of the detected smear-positive cases [4].

Since 1995, the Damien Foundation (Belgium) has being assisting the DOT centre of the University College Hospital, Ibadan to manage all cases of TB using the short-course chemotherapy (SCC) of the (NTBLCP) [5]. Through the United States' President's Emergency Plan for AIDS Relief (PEPFAR), additional funding has become available for the treatment of HIV-positive patients [6].

Due to the inadequate and inappropriate prescription of TB treatment by health practitioners coupled with the high default rate from treatment by patients as a result of the high cost of TB treatment in many private institutions some patients have recurrent TB which requires that they are commenced on re-treatment regimen (Category II regimen) in accordance with the current NTBLCP guidelines. In health institution where TB treatment is free poor drug compliance and non implementation of DOTS lead to recurrent TB.

Re-treatment is inevitable for patients with recurrent PTB, who defaulted on previous therapy and in cases where the initial treatment has failed. Many studies [7-10] indicate that a significant percentage of recurrent PTB causes may be attributable to relapse with the same *Mycobacterium tuberculosis* strain, particularly following recent completion of treatment. Lamert *et al* [11] in a systemic review suggest that re-infection per se may have few implications for TB control except in settings with considerably high incidence, while immuno-compromised patients are reported to be at greater risk of re-infection [12].

Poor patient compliance, increasing age, emergence of multi drug resistant mycobacteria and chronic alcoholism have been associated with re-treatment [13-15]. Additionally, HIV seropositive patients have generally been shown to have more frequent episode of recurrence compared to seronegative patients [7,9-11].

Since the commencement of the Directly Observed Treatment Short course (DOTS), which is the WHO recommended strategy for TB control globally, the impact of the programme with regards to the treatment outcome among patients with recurrent PTB has not been assessed. This study was undertaken to evaluate the treatment outcomes in patients started on re-treatment. drug regimen and the adequacy of the currently advocated re-treatment drug regimen in Ibadan.

Materials and methods

A five year retrospective study was carried out between April 2003 and March 2008 at the Medical Out-Patient (MOP), UCH, Ibadan, Nigeria. The study was to evaluate the treatment outcome for the retreated smear positive pulmonary TB cases aged 15 years and above, who were also screened for HIV infection. The study was done at the Medical Out-Patient (MOP); UCH Ibadan, Nigeria. University College Hospital is a tertiary care centre in Ibadan where patient are referred from all over the country.

Case ascertainment

Patients who attended the clinic were made to produce three sputum samples out of which two were "on the spot" supervised and one early morning for Ziehl-Neelsen test. They were also made to take a chest x-ray to document evidence of PTB. Screening for HIV status using enzyme linked immunosorbent assay (ELISA) was carried out and positive tests were confirmed by Western Blot. The ELISA procedure is as follows – The ELISA screening test was done on an automated pipetting and analysing machines with 96-well microlitre plates. It was based on the principle of HIV antigen-antibody

reaction using a mixture of recombinant synthetic peptides to represent immunodominant epitopes. The viral antigen bound to the bottom of the wells in the microlitre plate and upon addition of patient serum containing HIV antibodies, antigen-antibody binding occured. This reaction was detected by the addition of an enzyme-labelled "conjugate" which bound to the antigen-antibody complex. The enzyme contained in the bound conjugate then acted on a substrate added in the final step of the procedure, there would be a colour change if HIV antigen-antibody reaction had taken place earlier on in the wells of the microlitre plates. The intensity ("optical density", O.D.) of this colour reaction was measured and was proportional to the antibody activity in the sample.

The medical records of all patients with re-treatment therapy were reviewed The patient was considered smear positive if at least two sputum specimen were positive for acid-fast bacilli(AFB) by microscopy, or a patient with only one sputum specimen which was positive for AFB by microscopy and chest radiographic abnormalities consistent with PTB. Information also collected included age, gender, height, weight, history of TB treatment, HIV status and outcome of treatment.

Treatment regimens

The regimen used consisted of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z) and Ethambutol (E) and Streptomycin(S) in the first two months (2SRHZE) followed by another month of RHZE as the intensive phase followed by continuation phase of five months of Rifampicin, Isoniazid and Ethambutol. This is the Category II or re-treatment regimen for relapses, failure and return after default(RAD) in accordance with the NTBLCP. (b). The HIV patients were on the first line drugs consisting of Stavudine(d4T), Lamivudine(3TC) and Efavirenz(EF)

Follow-up and outcome analysis

For the purpose of this study, the definitions of treatment outcome were as follows:

1. Cure: A patient who was smear positive at diagnosis, who completed eight months of therapy and who is smear-negative at the end of 7th month of treatment and at least one previous occasion
2. Treatment completed: Any patient who was smear-positive at diagnosis and who completed treatment but in whom smear examination results were not available at the end of treatment.
3. Died: Any patient who died for any reason during the course of his/her chemotherapy.
4. Defaulter: Any patient who has interrupted for eight consecutive weeks or more after the date of the last attendance during the course of treatment.
5. Transferred out: A patient who was transferred to another treatment centre in another state and whose treatment was not known.

Statistical analysis

Data were coded and analyzed using the statistical software SPSS Version 10.0 (SPSS Inc, Chicago IL). Descriptive statistics such as means and standard deviations were summarized with proportions and percentages, Chi-square and Fisher's exact tests (where necessary) were used to measure the associations between discrete variables. All analysis was done at the 5% level of significance

Results

Age and sex distribution

In total data of, 127 re-treatment PTB patients were analyzed during the five-year period of study comprising of 69(54%) males and 58(45.7%) females. Their ages ranged between 15 and 65years. The mean age in males was 39.33 ± 15.52 and 37.12 ± 15.44 in females.

Table 1: Age and sex distribution of patients on the re-treatment regimen

	Sex			
Age (yrs)	Male	(%)	female	(%)
< 20	7	5.5	3	2.4
20 - 29	14	11.0	16	23.6
30 - 39	18	14.2	20	29.9
40 - 49	14	11.0	11	19.7
50 - 59	5	3.9	3	6.3
> 60	11	8.7	5	12.6
Total	69	54.3	58	45.7

Table 1 shows the age distribution of the patients. Ten (7.0%) patients were aged less than 20years, 93(73.2%) aged between 20-49 years and 16(12.7%) aged 60years or more.

Treatment outcome

The outcome of treatment is shown in Table 2. In total, 81 (63.8%) patients were cured and 13 (10.2%) completed treatment. The addition of the percentage of patients that completed treatment and cured is the percentage of treatment success which is 74%, 22

(17.3%) Died; 4 (3.1%) defaulted while 7 (5.5%) were transferred out

Table 2: Treatment outcome among patients treated for re-treatment tuberculosis

Outcome	Frequency N = 127	Percentage (%)
* Treatment Success	94	74.0
Cured	81	63.8
Treatment Completed	13	10.2
Died	22	17.3
Defaulted	4	3.1
Transferred Out	7	5.5

**Treatment Success = Cured + Treatment Completed*

HIV seropositivity and age distribution

Out of 127 subjects studied, 42 were confirmed HIV positive giving a seroprevalence of 33.1%. Majority of the patients with HIV positivity fell between the age of 20-49 years accounting for 76.2% of all the subjects that had retroviral infection.

Death

In total, 22(17.3%) patients died over the five-year follow up. More deaths were recorded among the HIV positive patients 13 (59.1%) than the HIV negative ones, nine (46.9%).

Table 3: Treatment outcome and HIV status of the patients on re-treatment therapy

	HIV Status			
Treatment Outcome	Positive	(%)	Negative	(%)
* Treatment Success	27	21.3	67	52.8
Cured	25	19.7	56	44.1
Treatment Completed	2	1.6	11	8.7
Died	13	10.2	9	7.1
Defaulted	1	0.8	3	2.4
Transferred Out	1	0.8	4	4.7

Cured and treatment completed

The 81% patients cured, 56(69.1%) were HIV negative, while 11(84.6%) completed treatment compared with two (15.4%) among the HIV positive patients. The treatment success rate was therefore higher in HIV negative PTB subjects compared with the seropositive ones.

Transferred out and defaulted

Few number of patients belong to these categories accounting for 5.5% and 3.1% of total patients respectively and more with HIV negative than positive patients.

Discussion

Re-treatment PTB appears to be a major concern, making it an important contribution to the burden of pulmonary disease in this tertiary health centre. The preponderance of males (54%) in this study is consistent with previous studies in this environment [5,6]. Ige *et al* [6] in the same centre reported that males were more affected than females. Mohamed S. Al Hajjaj [16] in his study and Erhabor *et al* [17] in Ife, Nigeria also documented that male patients outnumbered female patients among the Saudi nationals and Nigerians respectively. The gender distribution of PTB patients enrolled in the survey of HIV infection among patients with PTB in Nigeria by Odaibo *et al* [18] shows that more males (63%) than female (37%) subjects presented with PTB in all the geopolitical zones and states with the exception of Lagos state that had equal rate. The very high male to female ratio among PTB patients observed in this study may indicate difference in accessibility or utilization of health facilities by male and female population groups in this country.

In this study majority of the patients with re-treatment PTB aged between 20- 49years making 73.2% of all the patients and patients above the age of 60 years account for 12.7% of cases. This is consistent with the finding of Odaibo *et al* [18] who observed that 71% of the PTB patients recruited for the National Survey Program were in the age range of 20-40 years. These population groups constitute the most productive sector of a nation, but now over burden with PTB in Nigeria. It is therefore possible that exposure to PTB may be due to work related activities involving over crowding and close contact by this most active group of the population in the country. This explanation becomes more plausible by the fact that more male than female subjects presented with PTB in this study

The finding of re-treatment PTB cases among patients above 60years of age in this study is in keeping with findings of Norbert *et al* [19] who documented a high frequency of re-treatment PTB among older patients at two teaching and referral hospitals in Uganda. Re-infection may have a role to play as there is an increased risk of new infection with age in high incident setting [19]. Moreover, HIV infection together with

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progressive immuno-suppression with age, increase the development of active disease following re-infection of mycobacteria [20,21].

The seroprevalence of HIV co-infection among the re-treatment PTB cases was 33.1% which is higher than recorded seroprevalence of 28.1% by Ige *et al* [22] at the same centre. This is most likely due to the fact that previous study was conducted among the newly diagnosed PTB cases. For the same reason Salami *et al* [23]; Akinsete *et al* [24]; and Daniel *et al* [25] had seroprevalence rates of 12.6%, 15.5% and 14.9% respectively.

The treatment success rate of 74% observed in the study is similar to 76.3% and 78% reported in Mali [26] and Benin respectively [27]. The success rate observed in this study was lower than the WHO recommendation of 85% possibly because these patients presented late for treatment in this center after initial treatment at their referral centres.

Achieving this percentage success rate in this study meant that the strain of mycobacterium is still susceptible to the current treatment approach in patients with recurrent TB in our centre. There is however, the need to carry out drug resistance survey by sputum culture and drug susceptibility testing (DST) among patients with recurrent PTB so as to give them appropriate treatment. This will not only reduce the incidence of drug resistant TB including multi-drug resistant TB but also identify the drug resistance pattern and monitor the trend over time in this centre

The defaulter rate of 3.1% observed in this study is very low and encouraging when compared with two earlier studies that documented higher defaulter rates of 10% and 17.7% respectively [27,28].

The low defaulter rate is an encouraging finding in this study because those defaulting from treatment constitute a reservoir pool of drug resistant strain of mycobacterium tubercle that can be transmitted within the community leading to a high incidence of primary resistance to standard short course chemotherapy among newly diagnosed patients.

The current guideline makes no provision for patients who fail re-treatment regimen [29], this may lead to the continued transmission of multi-drug resistant TB strain in the community. The introduction of DOTS-Plus strategy [29-34] recommended by WHO for the treatment of drug resistant TB using the second-line drugs may be necessary in this category of patients to prevent the spread of multi-drug resistant TB (MDR-TB).

The success rate was significantly related to the HIV status which is in agreement with the finding from previous studies that reported that HIV status was associated with poorer outcome among TB patients on re-treatment regimen [35,36]. HIV positive status is still a major factor contributing to the low level of treatment success in Nigeria.

Limitations

No data was readily available on repeat sputum smears, Therefore, the proportion of re-treatment PTB attributable to treatment failure could not be quantified. This is because pulmonary TB patients were reported to normally "dry up" quickly, implying that production of sputum ceases soon after initiation of treatment. In addition, the contribution of anti-mycobacteria drug resistance could not be ascertained as culture and DST to the first line drugs were not done

Conclusion

Re-treatment TB is frequent at this referral hospital where the success rate is lower than the WHO recommendation of 85%. The need for proper management of new TB cases using DOTS should be re-emphasised to alter this trend and also prevent development of MDR TB.

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