

Evaluation of the efficacy of directly observed treatment short course (DOTS) in patients with tuberculosis and HIV Co-infection in Kano, Nigeria.

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Abstract

Background: A prospective study to assess the outcome of the directly observed treatment short course (DOTS) in tuberculosis patients with HIV co – infection was conducted in Kano, Nigeria between 2005 and 2006.

Methods: The study group included one thousand six hundred and ninety two Tuberculosis patients (1066 men and 626 women) aged 15years and above. The recruitment protocol involved patients clinically diagnosed by X – ray and Mantoux test but with no previous tuberculosis treatment whose initial sputum demonstrated acid fast bacilli (AFB) on at least two occasions as confirmed by Ziehl Neelsen techniques and microscopical procedures. HIV serostatus was confirmed using HIV-1/HIV-2 ELISA Capillus, Geni-II HIV1/HIV2 kit and Determine HIV1/2 protocols. Standardized treatment regimen containing isoniazid, rifampicin, pyrazinamide and ethambutol were administered to the in patients for two months as intensive phase under the researchers direct clinical observation and monitoring. Treatment and follow up continued to the eighth month while the outcome of cure, were assessed using standard protocols.

Results: A total of six hundred and fifty (38.4%) sputum smear acid fast bacilli (AFB) positive patients (391 male and 259 female) were found to be sero positive for HIV. Treatment success rates after completion of dose regimen was 40% (261), of which 91% were sputum negative for AFB after the first treatment phase of two months. This increased to 94% and 97% by the 5th and 8th month respectively.

Conclusion: An incidence of 38.4% of HIV/TB co-infection was reported at the Kano State Government officially designated Infectious Disease Hospital (IDH) Kano (2005 – 2006). However, chemotherapy by DOTS was able to cure only 40% of patients, indicating efficacy much lower than the 85% targeted by the World Health Organization(WHO). Thus, new regimens and administration protocols are needed.

Keywords: Tuberculosis / HIV Co – infection, chemotherapy DOTS, Nigeria

Introduction

Tuberculosis is an air borne infection caused by the tubercle bacillus *Mycobacterium tuberculosis* [1]. It is a global health priority being a killer disease that manifests in its pulmonary form in up to 70% of cases or as extra pulmonary affecting all parts of the body [2]. An estimated seven million new cases occur each year, resulting in 2 – 3 million deaths despite being curable and preventable with effective treatment regimens and vaccines [3]. Improvement in case identification and compliance with appropriate treatment remains a major challenge [3]. Nigeria as the most populous country in sub-Saharan Africa, carries the highest burden of tuberculosis and has placed it among the top five of the WHO 22 high burden tuberculosis countries [3]. Available data reported that about 200,000 of all types and 100,000 of new sputum positive

tuberculosis occur each year with an estimated 2% annual risk of infection in Nigeria [4]. A study in Calabar, Cross River State, Nigeria also recently showed no decline in the intensity of the disease inspite of DOTS [5]. Globally sub – Saharan Africa has the highest rate of tuberculosis as well as HIV/AIDS [3]. Today almost 70% of those co – infected with tuberculosis and HIV/AIDS live in Africa. The high rates of Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) have caused a sharp rise in the prevalence of tuberculosis [6]. For example in Kenya, the number of new TB cases is increasing at the alarming rate of 12% each year. In Nigeria, Ethiopia, and South Africa the rate is increasing at 7% annually. This was in contrast to a global annual rate of increase of TB of just 0.4%. HIV/AIDS is the single most

important factor fuelling the increasing incidence of TB over the last decade [5, 6]. The profound immune suppression of HIV infection on active TB, has also increased the rate of recurrence of tuberculosis [7, 8]. Another study in Nigeria showed a median HIV prevalence of 17.0% (range 4.2% - 35.1%) among the TB patients. The highest prevalence was recorded in the north central state of Benue and the least was at the South-West state of Oyo [9]. Kano state recorded 12.4% in that survey [9]. This ranks the state as one of the vulnerable TB/HIV regions in Africa [10]. In a study in Maiduguri Nigeria, a 69.4% mycobacterium infection among HIV-seropositive patients was reported [11]. A similar study in Jos, Nigeria reported a 12.6% rate of HIV/TB co-infection [12]. The global increase in the problem is not a lack of an effective treatment but that of properly applied short course chemotherapy. The WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) have recommended Directly Observed treatment short course (DOTS) strategy for the control of tuberculosis [5,10]. The essential features of DOTS strategy include government commitment to the TB control program, a secured supply of drugs, diagnosis based on sputum smear examination by microscopy in symptomatic patients, a reporting system and supervision of short course therapy using isoniazid, pyrazinamide and ethambutol including rifampicin in at least the intensive phase of treatment [13]. Treatment success in DOTS remains much higher than in non DOTS areas [13]. The DOTS strategy can be successfully implemented in even difficult conditions as those found in Cambodia [14]. Each country is to identify based on the local information, the combination of drugs to be used for the DOTS. Nigerian National Tuberculosis and Leprosy Control Programme in line with the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) recommendation have defined for new cases treatment (Category 1); that is, two months of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol as intensive phase, and 6 months continuation phase using Isoniazid and Ethambutol. These drugs can be used as loose or in fixed drugs combination [15]. For adequate tuberculosis treatment, an appropriate combination of anti - tuberculosis drugs taken regularly by the patients under direct observation for the prescribed period of time is required [15]. Studies on treatment outcome of human pulmonary TB patients with or without HIV Co - infection have been reported from elsewhere in Nigeria [15]. For example a study conducted in Sagamu, South western Nigeria, showed a cure rate of 76.8% although still lower than the World Health Organization recommended target of 85% [17]. The trend of pulmonary TB in-patients seen at six DOTS clinics in the Federal Capital Territory, Abuja Nigeria demonstrated a high prevalence of infectious TB in the population screened [18]. The authors alleged development of resistance to current anti - TB drugs. However, such cohort studies in Kano northern Nigeria are yet to be reported. It is relevant to evaluate the efficacy of DOTS regimen for tuberculosis in patients with HIV co-infection in a resource

limited country like Nigeria where TB is a leading cause of death. This is of particular importance to Global HIV control programme. It is in line with these needs that the present study was conducted for the first time in Kano, an area in Northern Nigeria with particular emphasis on evaluating the efficacy of DOTS regimen and the outcome of sputum smear positive pulmonary tuberculosis patients with the HIV co - infection attending the Infectious Diseases Hospital in Kano Nigeria (2005 - 2006).

Material and methods

Study Area

The study area was Kano state in northern Nigeria. It is located within savanna, latitude 12⁰ to 12⁰ 15' N and longitude 8⁰ 30' to 45¹ E. It has an elevation of about 525 meters above the sea level with a population of 12.4 million.

The Hospital for the study

The study was carried out between January 2005 and August, 2006 at the Infectious Diseases Hospital (IDH), Kano. It was the main Kano State Government official hospital designated to treat and manage infectious diseases. The hospital receives patients from the whole of Northern Nigeria, and serves as referral center for tuberculosis and HIV/AIDS control activities not only for Kano and other neighboring states but also for Niger and Cameroon republics. All Tuberculosis and HIV/AIDS related medical care are provided free of charge to the patients at the hospital, which has a chest clinic, that runs everyday and receives an average of 200 patients a day. There are wards for in-patients admission, laboratory services, HIV counseling and testing center, and TB and HIV collaborative activities.

Subjects for the Study

The subjects were both male and female patients that presented to the Chest Clinic with symptoms of pulmonary Tuberculosis based on the history and clinical examination and whose initial sputum smears demonstrated acid fast bacilli (AFB) by direct smear sputum on microscopy using Ziehl - Nelsen stain at least on at least two occasions in line with the recommendations of WHO [19,20]. The subjects are confirmed as TB patients through standard clinical and diagnostic investigations which are described as follows.

Clinical and Diagnostic Features for TB Investigation

Routine Chest X - ray was carried out on the suspected patients who presented with chronic deep seated productive cough with or without haemoptysis and Bronchopneumonia. This was followed by Tuberculosis testing with 10 units of tuberculin administered subdermally by Mantoux technique [20]. TB was

suspected when a positive Mantoux showed ≥ 5 mm induration. Chest X – ray film was carried out to evaluate for primary tuberculosis. Evidence of hilar gland enlargement, thousands of small nodules, millet size all of similar size and distributed through out the lungs confirmed Miliary TB. The presence of lung cavitations as mark of post primary TB [20] was also assessed. The method confirmed presence of Acid fast bacilli (AFB) in the sputum that was expectorated from a deep cough of the suspected patient [19, 20, 21].

Subject Selection Criteria

The subjects for the study were selected based on certain criteria, this is because of the need to have patients who can be relied upon to complete full duration of the treatment and the finding of the study will be applicable to a large population. Eligibility and exclusion criteria are presented in the following checklist [19, 20, 21].

Eligibility Criteria

- Patient should be:
- ≥ 15 years old
 - TB sputum positive
 - HIV seropositive
 - Living in Kano State
 - Willing for ambulatory treatment
 - Available for follow – up for the period of study

Exclusion Criteria

- On previous TB treatment
- On antiretroviral treatment
- In a moribund state
- With extra pulmonary TB complication
- With diabetes mellitus

HIV Counseling and Testing procedure

Each patient's informed consent to participate in the study was sought for and was offered confidential HIV testing accompanied by pre and post test counseling according to National AIDS Programs guidelines. Those that agreed to be tested had blood sample taken for HIV test. The investigation was performed according to the standard hospital practice and followed guidelines developed by the National HIV Rapid Test Algorithm. The ELISA Test of Capillus HIV-1/HIV-2 (Trinity, Biotech, Ireland); Genie II (HIV-1/HIV-2 test kit Bio-Rad Laboratories France) and Determine HIV1/2 (Inverness medical, UK) were followed [14,15]. HIV serostatus was recorded as positive if Capillus and Genie II tests were positive. Otherwise the result was negative if both Capillus and Genie II were negative. When the two tests showed discordant result (that is Capillus and Genie II did not agree, one being negative

and the other positive) the HIV status was recorded as indeterminate. The indeterminate result was then resolved by a tie – breaker which is Determine. This confirms the final result as positive or negative for HIV [15, 16]. All the patients that refused HIV testing after counseling and those with indeterminate results were excluded from the study.

Specimen Collection and Microscopy

The patients submitted three sputum specimens over two consecutive days. The first smears were prepared, fixed and stained by Ziehl – Neelsen staining methods for acid fast bacilli (AFB). The smears were examined for acid fast bacilli under oil immersion (x 100) objective [19, 20, 21].

Treatment and Follow-up of Patient

A category I standard regimen of never previously treated cases comprising of ethambutol, isoniazid, rifampicin and pyrazinamide was used for the treatment of smear positive cases as recommended by the International Union against Tuberculosis and Lung Diseases (IULTD) and World Health Organization [8] and as demonstrated in Sagamu southern Nigeria [4,17].

Intensive phase of treatment

All subjects were admitted to the test ward of the hospital for two months. Treatment was administered by DOTS regimen. The patients swallowed the tablets under the supervision of a health worker. Fixed drugs combination tablet of Pyrazinamide, Rifampicin, Ethambutol and Isoniazid, were used. Subjects were discharged after the two months intensive phase. The initial phase of treatment was prolonged by one month in case of smear positivity. At the end of the prolongation, another sputum smear was examined and the continuation phase started irrespective of the latter result. Continuation phase and their duration remained unchanged despite prolongation of the initial phase [4, 17, 21].

Continuation phase of treatment

This entailed a monthly collection by the patients at the DOTS clinic for six months. Self administered fixed drugs combination of Ethambutol and Isoniazid were used. The return of empty blister of packs of drugs signaled completion of treatment [4, 17, 21].

Monitoring of Patient

The sputum, of all the patients were re-examined at second, fifth and seventh months and two smears were taken one over night and one on the spot [21].

Treatment Outcome

Treatment outcomes as recommended by WHO and the IUATLD, and adapted in Nigeria [17, 21, 22] were categorized as cured, treatment completed, treatment failure, died, defaulted or transferred out. A patient was considered as “Cured” if a negative sputum smear (without AFB) was obtained in the last month of treatment and at least one previous occasion. A patient was considered as having “Completed treatment” if treatment had been completed and smear examination results were available at the end of the treatment. “Treatment failure” was marked by becoming AFB sputum positive again at least five months after the commencement of treatment. A “Defaulter” was a patient who did not return to collect the anti-tuberculosis for 8 weeks or more after the date of the last attendance during the course of treatment. A “Transferred out” was defined as a patient who was transferred to another reporting unit and for whom the treatment result was unknown [23] Death was reported for patients who died during treatment, regardless of cause.

Statistical analysis of the Data

Treatment outcomes between different groups were compared using Chi – square (X^2) test with difference at the 5% probability being regarded as significant. Descriptive statistics (numbers, percentage and means) were used in the analysis of data [24].

Results

Enrolments

For the two year period of study, a total of 1,844 patients with sputum smear positive tuberculosis were enrolled. Of these, 42 patients were not counseled for HIV testing during the two months period of admission, 79 refused HIV testing after counseling, 19 refused admission in the ward, and in 12 patients, the result were indeterminate. All these 152 patients

Table 1. The distribution of HIV/TB coinfectd patients on DOTS by age and gender at Infectious Disease Hospital, Kano Nigeria in 2005 – 2006.

Age	HIV/TB Male	HIV/TB Female	Total HIV/TB
15 – 24	74	40	114
25 – 34	179	112	291
35 – 44	90	79	169
45 – 54	40	22	62
55 – 64	7	4	11
65	1	2	3
Total	391	259	650

Table 2. Sputum conversion rate of seropositive TB patients at Pretreatment 2, 5 and 7months after treatment with standard chemotherapy (DOTS)

Number (%) positive for TB

HIV Status	Initial	2 months	5 months	7 months
Seropositive	650(100)	59(9)	39(6)	19(3)
% without AFB	0.00	91.00	94.00	97.00

Table 3. DOTS Treatment Outcome of TB/HIV seropsitive Patients in Kano Nigeria (2005-2006)

TB treatment Outcome	Cured	Failure	Transfer	Completed	Default	Death
No. of HIV patients n = 650 (100%)	261(40)	39(6)	18 (3)	172 (26)	57 (9)	103 (16)

were excluded from the study.

Demographic Data

The study identified a total of 650 TB patients that were HIV-seropositive (Table 1). This HIV seropositive – TB cohorts was made up of 40% females and 60% males. Although not statistically significant (gender versus HIV positivity; $X^2=3.67$; $P=0.055$), there was a higher proportion of HIV/TB co-infected females (259), in comparison with males (391).

Sputum Conversion Rate

Sputum conversion after two months intensive phase was 91% and as treatment continued to the seventh month only 3% of patients remained as TB (AFB) positive (Table 2).

Treatment outcome

The treatment outcome at the end of 8 months revealed that 40%(261) became cured. Treatment was completed by 26% (172). Treatment failure was recorded in 6% (39). A default of 9%(57) was observed, while transfer out was 3% (18) and 16%(103) deaths were recorded (Table 3).

Discussion

The treatment of tuberculosis especially when complicated by HIV seems to be difficult even with DOTS therapy [4,5,17,18]. The success rate of 40% obtained from this study is less than the global targets of 85% [17,23]. However, this can be

considered to be impressive in view of the much lower success rates recorded before the introduction of the DOTS programmes. Slightly greater success was reported in one study in Ilorin, Nigeria, that observed a 43.7% cure rate [21]. Another Study in Sagamu reported a 76.8% success [17]. However, in Calabar south- eastern Nigeria 42% cure rate was found [5]. The lower success rate of 40% recorded in this study resulted into a significantly high death rate of 16% among HIV positive patients. Progress in implementing effective tuberculosis control based on the DOTS strategy has been slow; by 1999, only 40% of estimated treated new cases were reported to WHO (23% in DOTS programmes and 17% in non DOTS programme) [16]. Many countries are failing to achieve adequate treatment outcomes due to patients default, transfer, and reinfection and in some cases high death rates [7]. Eventhough, outside the domain of the current investigation, it was argued that perhaps, the Problem of malnutrition among the patients could be a leading cause of the failure of DOTS [5]. This was obviously not different from virtually all the available reports from Nigeria [4, 5, 11, 12, 21]. In this study, sputum conversion was found to be 91% in the first two months of intensive phase. This is similar to a study in Uganda where

sputum conversion at the end of 2 months was similar for HIV positive and negative patients [16]. The high sputum conversion rate for HIV positive patients is an indication that the DOTS has the capacity for achieving good results even in settings with high HIV prevalence. Sputum conversion at 2 months is associated with good treatment outcomes. The study confirms that the possibility of reaching a cure which is higher among patients whose sputum has converted to AFB smear negative than among those whose sputum remains positive after the first two months of treatment which resulted in over 90% of patient showing no AFB. In Madagascar, the majority of failures were observed in patients who were smear positive at 2 months [22,23] Sputum conversion during the third month of treatment is an important predictor of treatment success [25]. This is in spite of the fact that some studies have demonstrated that HIV seropositive status is not a principal factor in delaying sputum conversion among patients receiving intensive phase tuberculosis treatment [26]. The sputum conversion rate at the fifth month was 94.0% and rose to 97% by the seventh month of therapy. However, 19 patients (3%) had delayed sputum conversion as noted at seventh through the eighth month. In conclusion, we found, an incidence of 38.4% of HIV co- infection among people with AFB positive smears attending the Infectious Diseases Hospital Kano, Nigeria (2005 – 2006). The study also showed a less than 50% cure rate which indicates a low efficacy of DOTS. Although there was a high (91%) sputum conversion rate in the intensive phase, only 40% cure rate was achieved after 8 months of therapy. This is lower than the WHO target of at least 85%, suggesting either an inadequate duration of treatment or loss of efficacy, perhaps due to drug resistance. A further need to improve the existing regimen with a better combination that could be more promising and cost effective is therefore advocated.

Authors' contributions

Ymuhammad (MD) conceived of and conducted the study under the supervision of TI Oyeyi (PhD, Assoc.Professor) as part of his research work for a PhD degree from Bayero University, Kano, Nigeria. MD Mukhtar (PhD, Assoc. Professor) internally supervised the work up to completion and drafted the manuscript. All authors read and contributed to the final version of the manuscript.

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