ORIGINAL ARTICLE

Treatment Outcome of TB/HIV Positive and TB/HIV negative Patients on Directly Observed Treatment, Short Course (DOTS) In Sagamu, Nigeria

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ABSTRACT

Objective: *The World Health Organisation marked 10 years of implementation of Directly Observed Treatment short course (DOTS). One key factor affecting the success of the DOTS strategy is the rising HIV prevalence among TB patients. The study was embarked upon to compare the treatment outcome of TB/HIV positive and TB/HIV negative patients in Sagamu, Nigeria.*

Methods: *A prospective study of 353 smear positive TB patients aged 15 years and above who were registered for 8 months anti-tuberculosis (DOTS) therapy between January 2001 and December 2003 at the Olabisi Onabanjo University Teaching Hospital, Sagamu, Nigeria. Treatment outcome indicators of cure, default, transfer to another district and death were assessed in relation to the HIV status of the patients.*

Results: *There were 353 eligible patients of which 58 (16.4%) were HIV positive. The clinical symptoms and signs of TB were similar in both HIV positive and negative TB patients. The cure rate was 76.8%.patients.The cure rate was significantly lower in HIV infected compared with non-HIV infected TB patients (60.3% v 80.0%;p=0.0001). However, among survivors it was not significant (71.4% v 82.5%;p=0.07). Overall mortality was 5.1% which was significantly higher in HIV positive compared to HIV negative TB patients (15.5% v 3.1%;p=0.00007). On the whole, 17% defaulted treatment and 1.1% failed treatment. These were however not significantly related to HIV status.*

Conclusion: *The cure rate in this study is still lower than the recommended 85% target by the WHO. Mortality rate in TB/HIV positive patients was higher than in HIV negative patients. The option of a community based TB programme using volunteers or family members to supervise administration of anti-TB drugs so as to ensure adherence to TB treatment may be considered.*

KEYWORDS: HIV; Tuberculosis; Outcome; Nigeria.

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INTRODUCTION

The World Health Organisation (WHO) marked ten years of successful Directly Observed Treatment Short course (DOTS) implementation for the control of tuberculosis in the year 2003[1]. The DOTS strategy aims at curing the individual patient, interrupts transmission of TB to other persons, and preventing the emergence of drug-resistant TB. In spite of the proven efficacy of this strategy only 27% of the world's TB patients are currently receiving DOTS[2]. The WHO set a global target of 85% cure rate and 70% case detection rate for TB control. In pursuance of this objective the Federal Ministry of Health through the National tuberculosis and leprosy control programme (NTBLCP) introduced the DOTS strategy for TB control in 1994[3]. Currently, a total of 432 of the 774 local government areas are implementing the DOTS programme in Nigeria through substantial donor support[4].

One of the major challenges facing TB control globally is the HIV epidemic. Presently up to 70% of patients with sputum positive pulmonary tuberculosis are HIV positive in some countries in Sub Saharan Africa[5]. The increasing frequency of TB/HIV co-infection has had considerable impact on TB control programmes in sub-Saharan Africa making the achievement of the 85% cure rate a big challenge. We have also observed an increasing prevalence of HIV infection among TB patients receiving the DOTS treatment programme in our centre[6,7]. The study was embarked upon to compare the treatment outcome of TB/HIV positive and TB/HIV negative patients in Sagamu within the current routine DOTS treatment programme for TB control in Sagamu, Nigeria.

MATERIALS AND METHODS

Study Population and Setting

This is a prospective study of patients admitted into the DOTS treatment programme at the department of community medicine Olabisi Onabanjo University Teaching Hospital (OOUTH), Sagamu. The study participants were recruited between January 2001 and December 2003. The study was carried out in Sagamu Local Government area in Ogun State. The town is a semi-urban area with an estimated population of 200,000 people[8]. It is located about 50km from Lagos and Ibadan, Nigeria. The German Leprosy Relief Association (GLRA) was responsible for the provision of

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free drugs for the programme. The centre provides DOTS for the treatment of tuberculosis on out- patient basis.

TB Control Programme

All tuberculosis patients who satisfied the inclusion criteria which consist of clinical symptoms suggestive of pulmonary tuberculosis such as cough, fever, haemoptysis, weight loss and night sweats; positive sputum smear for acid and alcohol fast bacilli by the Ziehl Neelson staining method, at least two times in line with the WHO recommendation; new cases (i.e. a patient who has never used anti-TB drugs before or used it for less than a month); adult patients aged 15 years and above: were included in the study. All patients were commenced on Short Course Chemotherapy (SCC) for a total duration of eight months. The SCC consists of two phases namely the intensive and the continuation phases. Four drugs namely, rifampicin, ethambutol, isoniazid and pyrazinamide were administered daily under supervision by a nurse during the intensive phase of two months. Patients were followed up monthly as out-patients for six months on ethambutol and isoniazid during the continuation phase. Any patient who failed to receive his/her treatment as scheduled was traced home by Community Health Extension Workers.

Laboratory Methods

All patients enrolled in the study were offered voluntary counselling and confidential testing for HIV screening by trained counsellors. The HIV antibody screening was done using two methods namely the immunocombs II HIV 1&2 Bispot test kit (Orgenics, France) and the Capillus HIV-1/HIV-2 kit(Cambridge diagnostics, Ireland). A positive test is considered only when the blood sample is positive for the two test kits. Sputum microscopic examination for Acid Fast Baccilli (AFB) was carried out at end of the 2nd, 5th and 8th months of chemotherapy.

Treatment Outcomes

The treatment outcome categories defined in the study was in line with the NTBLCP [9] guidelines. These include:

Died: death during TB treatment.

Cured: proven sputum smear negative after 8 months of therapy.

Default: failed to collect medication for more than 2 consecutive months after the date of the last attendance during the course of treatment.

Treatment failure: Sputum smear positive at five months or more after the commencement of anti-TB chemotherapy.

Ethical approval

The approval for this study was obtained from the OOUTH ethical committee for approval before the commencement of the project. Verbal informed consent was obtained from each patient before inclusion in the study.

Data analysis

Data analysis was done using standard statistical procedures with Epi info 2002 statistical soft wares. Differences between data were considered significant at P = 0.05. The differences between categorical variables were tested by Chi squared analysis. Survival analytical techniques were used to examine the effect of HIV sero-positivity on death rate. For analysis of death rate, survival rate curve was created to compare HIV positive and negative patients using the method of KAPLAN-MEIER (1958) [10].Cox proportional hazards regression was used to calculate the hazards ratio. Confidence interval at the 95% level was determined and statistical significance was at the 5% level.

RESULTS

Table I presents the socio-demographic characteristics of TB patients by their HIV status. A total of 353 sputum positive pulmonary TB patients were enrolled into the study. The male: female ratio was 1:0.99. Majority of the participants in the study had secondary school education and were Christians. Fifty-eight patients tested HIV positive (16.4%). In all, 24 men (41.4%) were HIV positive compared with 34 women (58.6%), the association was not statistically significant (p =0.13). The mean age of the HIV positive and negative men were similar (32.3 ±8.4 and 32.57 ± 13.7; p= 0.93).The mean age of HIV positive women was similar to HIV negative women (32.4±8.4 v 30.8±12.3;p=0.48). The mean weight at presentation was similar between HIV positive and HIV negative patients (48.8±7.1kg v 50.6±9.0kg:p=0.16).

Table II presents the symptoms of tuberculosis in relation to the HIV status. There was no significant difference in the distribution of clinical symptoms of TB such as cough, fever, weight loss, haemoptysis and chest pain in relation to HIV status.

Table III shows the treatment outcome in the patients under study according to HIV status. The overall cure rate was 76.8%.There was a strong association between HIV status and cure rate (60.3% v 80.0%:p=0.0001). However among survivors at the end of treatment the cure rate was no longer significantly

related to the HIV status (71.4% v 82.9% ;p=0.07).
Figure 1 shows the age distribution of the study population according to their HIV status. Eighty-one percent of HIV positive and 67.8% of HIV negative TB patients were in the age group 20-39 years while the least frequency was in the age group of =60 years which consist of 1.7% of HIV positive and 7.1% of HIV negative TB patients.

Overall, 60(16.7%) TB patients did not complete treatment. This was not related to their HIV status (22.4% v 15.9%;p=0.22). Forty (66.7%) were men while 20(33.3%) were women. There was no significant age difference between HIV positive and negative patients who defaulted treatment (p=0.49).
Four patients (1.1%) experienced failure of TB treatment, one (1.7%) HIV positive and three (1.0%) HIV negative the relationship was not significant.
Overall 18 (5.1%) patients died during treatment. Mortality was significantly higher in HIV positive compared to HIV negative TB patients (15.5% v 3.1%; p= 0.00007). HIV positive patients who died during treatment were significantly younger than HIV negative patients that died (30.8±7.1yrs v 50.3± 19.7yrs; p=0.01). HIV positive patients who died were of similar age to the HIV positive patients who survived (30.78±7.14yrs v 32.31±8.5yrs). There was no significant age difference between HIV negative patients who died and those who survived. After 8 months of follow-up, 71.4 % of HIV positive and 82.5% of HIV negative tuberculosis patients were still alive. The risk of death using the cox proportional hazard regression was 5.9 times for HIV positive than HIV negative patients (95% CI 2.3-14.9) which was statistically significant (p=0.0002) as shown in figure 2.

Table I. Socio -Demographic Characteristics of TB Patients by HIV Status at Sagamu between 2001-2003.

Characteristics	*HIV POSITIVE N=58 (%)*	*HIV NEGATIVE N=295 (%)*	*P-value*
SEX			
Male	24(41.4)	154(52.2)	
Female	34(58.6)	141(42.8)	0.13
Educational status			
No formal education	6	48	
Primary	19	46	
Secondary	31	174	
Tertiary	2	27	0.01
Religion			
Christianity	46	187	
Islam	12	108	0.02

Table II. Clinical Symptoms of TB at Presentation among Pulmonary Tuberculosis Patients According To HIV Antibody Status.

SYMPTOMS	HIV POSITIVE N=58(%)	HIV NEGATIVE N=295 (%)	$?^2$	P-VALUE
Cough	56(96.6)	285(96.6)	0.00	0.98
Fever	56(96.6)	290(98.3)	0.77	0.38
Weight loss	54(93.1)	281(95.3)	0.46	0.49
Haemoptysis	14(24.1)	104(35.3)	2.69	0.10
Chest pain	40(68.9)	218(73.9)	0.60	0.43
History of contact with TB	20(34.4)	83(28.1)	0.94	0.33

Table III. Treatment Outcome among Pulmonary Tuberculosis Patients According To HIV Status.

TREATMENT OUTCOME	TOTAL N=353 (%)	HIV POSITIVE N=58 (%)	HIV NEGATIVE N=295(%)	$?^2$	P-VALUE
Sputum conversion at 2 months	317(98.1)	56(96.5)	270(91.5)	1.73	0.18
Cured	271(76.8)	35(60.3)	236(80.0)	11.43	0.0001
Default	60(17.0)	13(22.4)	47(15.9)	1.62	0.22
Treatment failure	4(1.1)	1(1.7)	3(1.0)	0.22	0.51*
Death	18(5.1)	9(15.5)	9(3.1)	17.34	0.00007
Cure(survivors)**	271(80.9)	35(71.4)	236(82.5)	3.63	0.07

*=Fischer's exact test
** = the number of patients that died during treatment was excluded from the denominator.

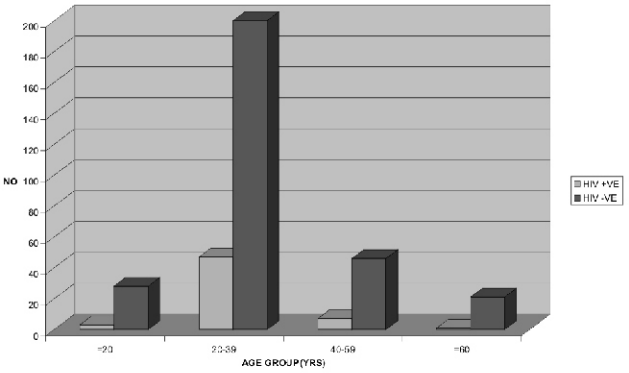

Fig. 1. Bar Chart Showing Age Distribution of HIV Positive and HIV Negative TB Patients in Sagamu

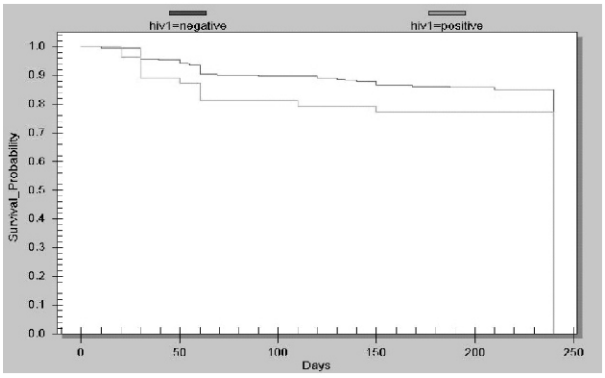

Fig. 2. Kaplan Meier Survival Curves for HIV Positive and HIV Negative Patients under Study.

DISCUSSION

The cure rate of 76.8% observed in this study is below the 85% recommended by the World Health Organisation. Similar studies have documented cure rates of between 80-85%[11-13]. In many of the studies with high success rate, several reasons such as the widespread use of voluntary lay supervisors to administer DOTS and the use of incentives to patients may have contributed to the high rates of treatment completion[12,14,15]. However, the cure rate was higher than the 43.7 % reported in a hospital based study in Northern Nigeria[16]. The disparity could be due to the late presentation of patients, fee charged for diagnosis and drug therapy and the absence of DOTS in the latter

study. This underscores the importance of the DOTS strategy in the control of tuberculosis in Nigeria. There is therefore a need for the decentralisation of TB treatment so that people infected with TB will have access to DOTS. Unlike previous studies however, the cure rate was significantly related to HIV positive status. The finding is similar to what was reported in South Africa gold miners[17]. HIV positive status is still a major factor contributing to the low level of treatment success in Nigeria

It was observed that case fatality rate was higher in HIV positive patients compared to HIV negative patients. This is consistent with similar studies conducted in Africa [18-20]. The cause of death could not be immediately ascertained because most of the patients that died during the study period died at home. This was mainly due to inability to afford hospital admission fee. Other studies have shown that the increased mortality during TB treatment was as a result of other bacterial infections[12,21] and the severe immunosupression[22] experienced by these patients before commencement of treatment. Hence some African researchers have advocated the use of co-trimoxazole prophylaxis to coinfected patients during TB treatment to reduce mortality and improve survival. [23] Also, concurrent administration of antiretroviral and anti-TB treatment in patients who meet criteria for the initiation of antiretroviral therapy have been associated with improved survival in TB/HIV coinfected patients[24].

The rate of default from treatment by the patients in this study was 17.0%. Default from treatment was higher in TB/HIV coinfected patients though the relationship was not statistically significant. We observed some reasons for default in this study. HIV patients who are severely ill tend to return to their home town to receive care and support from their extended family members. Secondly, some of the HIV patients leave the area to consult traditional and spiritual healers who advertise their infallible ability to cure HIV infection. Also, patients who were seriously ill could not come to collect their drugs personally and had no alternative arrangements available under the present government programme. Furthermore issues of stigma and discrimination forced some HIV positive patients to relocate especially those with HIV wasting syndrome and other obvious HIV related symptoms. Lastly, incorrect contact addresses or names made it extremely difficult to trace some of the patients who defaulted. The issues of discrimination and stigmatisation of HIV patients need to be addressed so as to ensure adherence to their TB treatment to improve survival. Family members can be used to as treatment partners to administer and monitor treatment especially when such patients are too ill and cannot come to collect their drugs personally. The provision of adequate logistic support to adequately trace defaulting patients is important to ensure success of the programme.

REFERENCES

1. World Health Organisation. WHO reports 10 million TB patients successfully treated under DOTS 10 years after declaring TB a global emergency. http://www.who.int/mediacentre/news/releases/2003/pr25/en.
2. Pearson B. DOTS still only reaching 27% of tuberculosis patients. African Health 2002;24(4):6.
3. Federal Ministry of Health and Social Services. TBL forum. National tuberculosis and leprosy control programme FMOH & SS Lagos Nigeria July 1994.
4. World Health Organization. WHO report on Global Tuberculosis Control. Geneva 2004.
5. Harries AD, Nyangulu DS, Kang'ombe C, *et al* Treatment outcome of an unselected cohort of tuberculosis patients in relation to human Immunodeficiency Virus sero status in Zomba Hospital, Malawi. Trans Roy Soc Trop Med Hyg 1998; 92(3) 343-347.
6. Daniel OJ. HIV sero-prevalence among newly diagnosed adult pulmonary tuberculosis patients in Sagamu Nig J Med 2004;13(4): 393-396.
7. Daniel OJ, Ogun SA, Salako AA, Oluwole FA. Frequency of HIV in TB patients attending tuberculosis and leprosy control centre in Sagamu. Tropical Doctor 2004;34(3):204 - 206.
8. National Population Commission 1991 Census. Population in States by sex and number of Households, 1995.
9. Federal Ministry of Health National Tuberculosis and leprosy control program .Revised workers manual. Nigeria 1998.
10. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. Journal of the American statistical Association 1958;53:457-481.
11. Kelly PM, Cumming RG, Kaldor JM. HIV and tuberculosis in rural Sub- Sahara Africa. A cohort study with two years follow up. Trans Roy SocTrop Med Hyg. 1999; 93(3): 287-293.
12. Wilkinson D, Davies GR, Connolly C. Directly observed therapy for tuberculosis in rural Africa, 1991 through 1994. Am J Public Health 1996; 86:1094 - 1097.
13. Nunn P, Brindle R, Carpenter L, et al Cohort study of Human Immunodeficiency Virus infected in patients with tuberculosis in Nairobi, Kenya. Analysis of early (6months) mortality. Am Rev Respir Dis 1992; 146: 849-854.
14. Westaway MS, Conradie PW, Remmers L. Supervised outpatient treatment of tuberculosis: evaluation of South African rural programme. Tubercle 1991;72(2):140-144.
15 Davidson N, Schluger NW, Feldman PH, *et al*. The effect

of increasing incentives on adherence to tuberculosis directly observed therapy. Int J Tuberc Lung Dis 2000; 4(9):860-865.
16. Salami AK, Oluboyo PO. Management of pulmonary tuberculosis: a nine year review in Ilorin. West Afr J Med 2003;22(2):114-119.
17. Mallory KF, Churchyard GJ, Kleinschnidt I, De cock KM., Corbett EL. The impact of HIV infection on recurrence of tuberculosis in South Africa gold miners. Int J. Tuberc Lung Dis 2000; 4(5): 455-462.
18. Lawn SD, Acheampong JW. Pulmonary tuberculosis in adult; factors associated with mortality at a Ghanaian teaching hospital. West Afr J Med 1999; 18(4):270-274.
19. Perriens JH, Colebunders RL, Karahunga C, *et al* Increased mortality and tuberculosis treatment failure rates among Human Immunodeficiency Virus (HIV) sero-positive compared with HIV sero-negative patients with Pulmonary tuberculosis treated with "Standard" chemotherapy in Kinshasa, Zaire. Am Rev Respir Dis 1991; 144:750 - 755.
20. Elliot AM, Luo N, Tembo G , *et al.* The impact of Human Immunodeficiency Virus on tuberculosis in Zambia, a cross-sectional study. Br Med J 1990; 301:412-415.
21. Perriens JH, St Louis ME, Mukadi YB, *et al*. Pulmonary tuberculosis in HIV infected patients in Zaire. A controlled trial of treatment of either 6 or 12 months. N Engl J Med 1994; 332: 779-784.
22. Ackah AN, Coulibaly D, Digbeu H, *et al*. Response to treatment, mortality and CD4 lymphocyte count in HIV infected persons with tuberculosis in Abidjan, Cote d'Ivoire. Lancet 1995; 345: 607-610.
23. Wiktor SZ, Sassan-Morroko M, Grant AD, *et al*. Efficacy of trimethoprim-sulphamethaxazole prophylaxis to decrease morbidity and mortality in HIV-I infected patients with tuberculosis in Abidjan, Cote d'Ivoire: a randomised controlled trial. Lancet 1999; 353:1469-1475.
24. Giradrdi E, Palmieri F, Cingolani A, et *al*. Changing clinical presentation and survival in HIV associated tuberculosis after highly active antiretroviral therapy. Journal of Acquired Immune Deficiency Syndromes 2001;26(4):326 - 331.