ORIGINAL ARTICLE

Outcome of Directly Observed Therapy Short Course (Dots) Regimen in A Rural Community of the Nigerian Niger Delta

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ABSTRACT

Bckground: The objective of this retrospective study was to evaluate the outcome of directly observed therapy short course (DOTS) application in a Nigerian rural community. **Methods:** A retrospective study of all the records of DOTS at the centre from January 2001 to December 2005 was compiled and features such as: age, gender, drugs used, and outcome of treatment (defaulted, cured, died, or developed multidrug resistant-TB) were considered. Also the different personnel and infrastructure at the centre for the programme were also assessed. Results were analysed using Epi Info 6 statistical software, and P values < 0.05 were considered significant.

Results: Two hundred and seventy four (274) cases of pulmonary TB were registered at the centre during the study period, consisting of 100(36.5%) females and 174(63.5%) males with a statistically significant gender difference (P<0.001). The age range with the highest number of pulmonary tuberculosis cases was 31-40 years (24.8%; n=68), and the age range with the lowest number was 71 years and above (1.1%; n=3). Treatment outcome showed that 84.7% (n=232) completed treatment with cure; 2.5% (n=7) developed multidrug resistance at completion of treatment; 5.5% (n=15) defaulted; 3.3% (n=9) died in the course of treatment, and treatment in 11 people was still ongoing.

Conclusion: The outcome of DOTS in the present study was impressive, and the programme should be extended to other rural communities; however, more efforts should be made towards the tracing of defaulters.

Key Words: DOTS, Rural community, Niger Delta, Nigeria

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INTRODUCTION

Pulmonary tuberculosis (PTB) is commonly caused by *Mycobacterium tuberculosis* which was first identified by Robert Koch in 1882. The organism is reported to have caused monumental loss of lives across the globe in the 16th, 17th, and 18th centuries such that, in the 17th century, it was aptly described by John Bunyan as "the captain of all

the men of death"¹. This trend of epidemic was however brought under control in several parts of the world such as-Western Europe, North America and Australia in the mid 70s and early 80s with the discovery of potent anti-TB drugs²⁻⁵. The control of tuberculosis was however not yet attained in most developing parts of the world such as Africa, Latin America, South East Asia and Middle East⁶⁻⁹, as a result of the socio-economic factors that are closely associated with the epidemiology of the disease¹⁰.

A new global trend of pulmonary and extra-pulmonary tuberculosis began to rear its head in the late 80s and early 90s even in those parts of the world where the disease had hitherto been under control, 11-12 in which the incidence and spread of the disease assumed a higher and more rapid dimension respectively. 13-15

At present, it is estimated that there are at least 60 million people worldwide with active tuberculosis, with not less than 3.3million new cases each year, 16, 17 and it is generally believed that the actual global figure would be far above this. Of the reported cases, 62% occurred in South East Asia and Western Pacific regions, 16% in sub-Saharan Africa, and about 8% in each of the regions of the Americas, Eastern Mediterranean and Europe. 18, 19 It is projected that between 2000 and 2020, if adequate control measures are not put in place, nearly 1 billion additional people will become infected by M. tuberculosis; 200 million will develop the active disease and 35 million will die from it. 16, 17 Findings from different parts of the world have shown a strong association between the spread of PTB and human immunodeficiency virus (HIV) infection. 20-22 TB has also evolved with various forms of unusual clinical pictures.²³

Over the past decade, several treatment modalities for TB have been proposed and experimented.²⁷⁻²⁹ The most universally accepted is that of "Directly Observed Therapy Short course (DOTS)", which ensures that the patient actually takes the medication under direct supervision of a nurse, (or a health assistant). This

treatment modality eventually emerged as a best solution to the problem of non-compliance, and has been found to be very effective in several parts of the world. 30-32

In Nigeria, DOTS has been adopted as one of Federal Governments' strategy to control the spread of TB in the country. This has the advantage of ensuring compliance and hence reducing the incidence of treatment failure as a result of the emergence of multidrug-resistant (MDR) *Mycobacterium tuberculosis* strains in an environment. DOTS at present is being expanded to cover Nigeria's 75% rural landscape in addition to the urban centres in order to ensure access to proper treatment.

The objective of this retrospective study was to evaluate the application of DOTS program in a Nigerian rural community. The findings will be useful as a guide to the success of DOTS and also to a large extent the control of TB in a Nigerian rural setting.

MATERIALS AND METHODS

Study Area: The study was carried out in Odukpani Local Government Area (L G A) of Cross-Rivers state, situated about 50 kilometres on the south-western part of Calabar, the state capital. The population of the local government area is estimated at 103,000 people based on 1991 population census. Being a riverine community, several of her inhabitants engage in fishing as a profession, a larger number engage in farming of crops such cassava and palm plantations, and a fewer people engage in timber business. Comprehensive Health Centre (CHC) Okoyong, an arm of the University of Calabar Teaching Hospital is sited in this LGA to render primary and secondary health care services to the people in the locality.

Study Design: The study is retrospective in nature and involves the compilation of data generated at the tuberculosis treatment centre at the CHC Okoyong at Ikot Effiong Otop in Odukpani L G A from January 2001 to December 2005.

Procedure: The data generated from the diagnosis of pulmonary tuberculosis, treatment, follow up and the final outcome of patients at the CHC Okoyong was compiled for the study period. An algorithm for tracking down suspected pulmonary tuberculosis patients is entrenched in the local governments' primary health centres (PHC), health posts, and private clinics in the locality. All patients with symptoms and signs suggestive of tuberculosis such as persistent cough (>three weeks),

night sweats, and weight loss at various health centres in the locality are referred to the CHC Okoyong for enrolment in the Directly Observed Therapy Short course (DOTS) program. Also all patients with cough that was unresponsive to the common antibiotics were also referred to this TB treatment centre for review and investigations.

All the referred cases were reviewed and thorough physical examination carried out by medical officers and senior registrars to establish diagnosis. Laboratory investigations such as sputum for AFB and Mantoux test were carried out where the need arose, Plain chest X-ray was also occasionally requested to aid in the diagnosis. Patients were also screened for HIV using the spot method (Determine). Also the personnel and infrastructure available for the programme were assessed.

Drug Therapy: The drugs used in TB DOTS program at C H C O k o y o n g w e r e R i f a m p i c i n (150mg)/Isoniazid(100mg) (RH) combined tablets, Pyrazinamide(400mg) (Z), and Ethambutol(400mg) (E). Patients were placed on this regimen daily for 2 months intensive phase, then for continuation phase of 6 months, H/E (150mg/400mg) combined tablets were given. Ant-TB drugs were given to patients on daily basis during the intensive phase and were swallowed in the presence of health personnel. During the continuation phase, patients were given drugs on monthly basis and on each visit; they had to swallow the dose for that day in the presence of the administering health personnel. Doses were appropriately adjusted for paediatric patients.

Follow Up: A chart is opened for every patient that commenced therapy to monitor daily compliance in the administration of the drug. At each follow up visit, patients are asked about any missed dose, and ticked in the chart appropriately. Also other problems that the patient the patient might have encountered in the course of taking the medications were also discussed and addressed appropriately. At the end of the intensive phase where patients have become sputum AFB negative, patients were then booked for monthly intervals for the continuation phase of DOTS therapy while intensive phase was continued on people who were still sputum smear positive. Sputum was examined for AFB at 5th and 7th months in the course of treatment. Measurement of weight and physical examinations were done during follow up visits.

Patients were certified cured from TB when they completed the DOTS regime, the signs and symptoms of TB cleared, such as absence of cough and chest symptoms, regained weight, and sputum smear negative for AFB at (or one month prior to) the completion of treatment and on at least one previous occasion³³. The community health extension workers (CHEW), community health officers (CHO) and nurses administered the drugs on daily basis under the supervision of the medical officers.

Analysis of Results: The results obtained were analysed using Epi Info 6 statistical software, Chi square (X^2) was used to compare association among variables, P values < 0.05 were considered significant.

RESULTS

From January 2001 to December 2005, 274 patients were diagnosed to have pulmonary tuberculosis and were enrolled into the DOTS programme at CHC Okoyong. The prevalence of HIV among the TB patients was found to be 38% (n= 104).

Table I shows the age and gender distribution of the patients registered for DOTS. The highest number was among those aged 31-40 years (24.8%; n=68), followed by 21-30 years of age group (24.1%; n=66), and then, 41-50 years (18.2%; n=50), while the age range with the lowest number were those with 71 years and above (1.1%; n=3). One hundred and seventy four (63.5%) of the patients were of males, while 100 (36.5%) were females (p<0.05).

Table II shows the outcome of DOTS implementation: 84.7% (n= 232) patients at completion of treatment were cured of PTB, 2.5% (n=7) completed treatment; 5.5% (n= 15) defaulted, 3.3% (n=9) were reported dead by their relations. DOTS was still ongoing in eleven patients.

Table I Age and sex distribution of pulmonary tuberculosis (PTB) patients on directly observed therapy short course (DOTS) regimen at Comprehensive Health Centre (CHC) Okoyong.

Age Group (Years)	Male (%)	Female (%)	Total	Percent
0-10	6(2.2)	1(0.4)	7	2.6
11-20	15(5.4)	6(2.2)	21	7.7
21-30	34(12.4)	32(11.7)	66	24.1
31-40	40(14.6)	28(10.2)	68	24.8
41-50	35(12.8)	15(5.4)	50	18.2
51-60	25(9.1)	11(4.0)	36	13.1
61-70	9(3.3)	3(1.1)	12	4.4
71 & Above	3(1.1)	0(0.0)	3	1.1
Unclassified	7(2.6)	4(1.5)	11	4.0
Total	174(63.5)	100(36.5)	274	100

Parenthesis=Percent X²=13.43, P<0.05

Table II Outcome of directly observed therapy short course (DOTS) implementation at Comprehensive Health Centre (CHC) Okoyong from January 2001 to December 2005

Treatment Outcome	Number	Percent
Treatment completed with cure	232	84.7
Treatment completed without cure	7	2.5
Defaulted	15	5.5
Died	9	3.3
Treatment ongoing	11	4.0
Total	274	100

DISCUSSION

Of the 274 patients recorded for DOTS in the present study, 36.5% were females and 63.5% males; (approximate M: F ratio of 2: 1). This finding is similar to that of Egah *et al* in Jos,³⁹ Peters & Ekott in Calabar,⁴⁰ Nigeria, and Cummings *et al* in California, USA⁴¹. The adventurous nature of males coupled with environmental and possibly genetic predisposition could, to some extent, account for this male preponderence.⁴²⁻⁴⁴

The prevalence of PTB was higher among those aged 21 to 60 years old and lower at the other extremes of age (those less than 20 years and those above 60 years). This pattern of distribution may be associated with the rate of exposure of the individual age groups to *Mycobacterium spp*; since the younger and the elderly generally have a restrictive pattern of movement and hence less exposure to infectious agents. ⁴⁵ Also the present AIDS pandemic which predominantly affects the youths and middle age group which are more sexually active could as well have played a significant role in the distribution of PTB in this locality; since cases of TB are higher in HIV infected patients who are immunosuppressed; ^{46,47} the 38% HIV seroprevalence found among them attests to this fact.

Establishment of DOTS centres at present in the country cannot be said to be complete without adequate provision for proper screening and diagnosis of HIV infection.⁴⁸ In addition to the provision of DOTS regime in the rural communities, simple HIV screening kits should also be supplied and patient friendly means of referral at nil or minimal cost to the patient be provided to aid easy transfer.

About 84.7% of those who completed their DOTS regimen at various times had cure. This treatment outcome is impressive and has shown a significant improvement over the traditional methods of treatment where the cure rate was in the range of 60% to 70% predominantly due to lack of drug compliance. 40,41 This finding from this study is similar to that of a multicentre

collaborative study on DOTS in China⁴⁹ where over 96% cure rate was achieved with a significant difference in treatment outcome compared to the traditional methods. Similarly, in a study carried out in Iwo, south west Nigeria,⁵⁰ a 100% cure rate was obtained, and in California,⁴¹ over 98% cure rate was recorded among those who completed their DOTS regime. In another study carried out in Enugu⁵¹ on home-based lay worker supervised, and facility based health worker supervised DOTS, 92% and 90% success rates were obtained respectively. Similar impressive treatment outcomes were recorded in studies carried out in Kaduna⁵² and Ethiopia.⁵³

The findings from this study underscores the need for the National Tuberculosis Control programme to establish more DOTS centres in the rural communities across the country. A scenario where there will be only one viable DOTS centre in a whole local government area does not augur well for the control of this national disaster. Sitting the TB centre at only one location in a local government area denies many people in the hinterland access to cure especially those who are already very sick and cannot trek long distances.

The findings of impressive outcome of DOTS regimen from this study are however different from that of Al-Hajjaj in Saudi Arabia⁵⁴ where it was found that the outcome of DOTS implementation in Saudi national tuberculosis control programme was not satisfactory; although there was significant decrease in default rate from 15% in 1995 to 1.2% in 1998, the over all cure rate was not significantly different. The unimpressive outcome was attributed to inadequate provision of infrastructure, personnel and logistics; the inability to obtain a 100% success rate in the present study may as well be attributed to these factors.

A default rate of 5.5% was obtained in our study; efforts to trace them failed. The TB treatment centre does not have TB-Home visitors or supervisors; also there were no facilities such as bicycles or motorcycles to aid the movement of such health personnel. This makes the movement into the hinterland and creeks to trace the defaulters difficult. This constitutes a serious public health problem, as without efficient mechanism to trace defaulters, who would continue to spread the infection in the community, the control programme will fail to yield timely results or even fail eventually.

In California, 41 a default rate of 5.5% was as well reported. While it was difficult to trace the defaulters in the Californian study, who moved from one major city to

another; proper health education of patients in the present study who are rural dwellers, recruitment of home visitors, and provision of bicycles and motorcycles to aid their movement in some difficult terrains would drastically reduce the rate of default.

Six of the seven patients that completed their 8 months of treatment without cure had problem with adherence. three had to go over intensive phase once again and the other three their continuation phase had to be prolonged by 3 months, however cure was not achieved; five of the patients were HIV positive. This problem of multidrug resistance was commonly encountered among patients with poor adherence to anti-tuberculosis drugs and MDR-TB has assumed a new dimension globally since the advent of the AIDS pandemic. 54, 55 These patients were eventually referred to University of Calabar Teaching Hospital Calabar. Apart from giving patients proper health education on adherence at commencement of DOTS and on subsequent follow up visits, home supervisors when available should as well emphasize the need for the patient not to miss a single dose in the course of treatment.

Nine patients died after the commencement of the DOTS regimen, eight were HIV positive. The death of four could be attributed to hepatic and other complications arising from the anti-TB drugs or HIV itself; three occurred during the intensive phase, one during continuation phase, while the other five were reported dead during the continuation phase of the treatment, possibly from complications of AIDS. The morbidity and mortality arising from TB could be drastically reduced if antiretroviral drugs were equally made available to these patients in the same manner as anti-TB drugs. ^{56,57}

In conclusion, this study has shown that the outcome of DOTS in a rural community if properly implemented is impressive and should therefore be sustained. There are however too few DOTS centres in the rural communities, and so more centres should be opened in each local government area to increase the proximity of the programme to the people. Also, TB home supervisors should be employed and equipped with appropriate facilities to aid their movement to trace defaulters, assist in patient compliance and strengthen community TB surveillance programme. It is only then that the present National Tuberculosis Control Programme would produce the desired results.

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REFERENCES

- Duguid JP, Marmion BP, Swain RHA. Mackie and McCartney Medical Microbiology: A guide to the laboratory diagnosis and control of infections. Vol 1, 13th Edn. U K Edindurgh: Churchill Livingstone 1978: 284-296.
- Moble-Boctani JC, Flood J. Contact investigations and continued commitment to control tuberculosis. J A MA 2002; 289(8):1040-1042.
- Tobin MJ. Tuberculosis lung infections, interstitial lung disease and socioeconomic issues in AJRCCM 2001. Am J Respir Crit Care Med 2002; 165(5): 631-641.
- Cainelli F, Vento S. BCG efficacy and tuberculin skin testing. Lancet 2002; 359(6): 1521-1522.
- 5. Dooley KE, Glub J, Goes FS, Merz WG, Sterling TR. Empiric treatment of community acquired pneumonia with fluoroquinolones and delays in the treatment of tuberculosis. Clin Infect Dis 2002; 34(12): 1607-1612.
- 6. Voljavec BF, Corpe RF. The influence of corticosteroid hormones in the treatment of tuberculous meningitis in Negroes. Am Rev Respir Dis 1960; 81: 539-545.
- Escobar JA, Belsey MA, Ducnas A, Medinea P. Mortality from tuberculous meningitis reduced by steroid therapy. Paediatrics 1975; 56: 1050-1055.
- Bastani B, Shariatzadeh MR, Dehdashti F. Tuberculous peritonitis: a report of 30 cases and a review of the literature. Q J Med 1985; 56: 549-557.
- 9. CDC-MMWR. Tuberculosis and acquired immunodeficiency syndrome. CDC-Morb Mortal Wkly Rep 1987; 36: 785-788.
- Lucas AO, Gilles HM. A new short textbook of preventive medicine for the tropics. 3rd Edn. U K, London: Edward Arnold Publishers 1990: 1-178.
- 11. Cobo J, Moreno S. Predicting tuberculosis at hospital admission. Arch Intern Med 2002; 162(5): 611-612.
- 12. Daniel IM. Origins of tuberculosis in North America. Clin Infect Dis 2002; 34(2): 291-294.
- 13. Gioia C, Agrati C, Casetti R, *et al.* Lack of CD27-CD45 RA-V gamma av delta 2+ T cell effectors in immunocompromised hosts and during active pulmonary tuberculosis. J Immunol 2002; 168(3): 1484-1489.
- Garcia MR, Rodriguez JC, Navarro JF, et al. Molecular Epidemiology of tuberculosis in Elche Spain. J Med Microbiol 2002; 51(3): 273-277.
- Heffelfinger JD, Davis TE, Gebrian B, et al. Evaluation of children with recurrent pneumonia diagnosed by World Health Organization criteria. Paediatr Infect Dis J 2002; 21(2): 108-112.
- Aristmuno L, Armengol R, Cebollada A, et al. Molecular characterization of Mycobacterium tuberculosis isolates in the first National survey of ant-tuberculosis drug resistance from Venezuela. BMC Microbiology 2006; 6: 90. http://www.biomedcentral.com/1471-2180/6/90
- 17. World Health Organization (WHO). Global tuberculosis control: Surveillance, Planning, Financing. WHO/HTM/TB/2006/362/Geneva.
- 18. Verver S, Warren RM, Munch Z, et al. Transmission of

- tuberculosis in a high incidence urban community in South Africa. Int J Epidemiol 2004: 33: 351-357.
- Van Rie A, Warren R, Richardson M, et al. Exogenous reinfection as a cause of recurrent tuberculosis after curative treatment. N Engl J Med 1999; 341: 1174-1179.
- Elsabban MS, Lofty O, Awad WM, et al. Bovine tuberculosis and its extent of spread as a source of infection to man in Arab Republic of Egypt. In the proceedings of the international union against tuberculosis and lung disease conference on animal tuberculosis in Africa and the Middle East 1992, April 28-30 Cairo Egypt. The Union 1992: 198-211
- Rose AM, Sinka K, Watson JM, Mortimer JY, Charlett A. An estimate of the contribution of HIV infection in the recent rise in tuberculosis in England and Wales. Thorax 2002; 57(5): 442-445.
- CDC-MMWR. Tuberculosis morbidity-United States, 1996.
 CDC-Morb Mortal Wkly Rep 1997; 46(30): 695-700.
- 23. Onipede AO, Idigbe O, Ako-Nai AK, *et al.* Seroprevalence of HIV antibodies in tuberculosis patients in Ile-Ife, Nigeria. East Afri Med J 1999; 76(3): 127-132.
- Oviawe O. Mortality of childhood tuberculosis in Benin-city, Nigeria. Analysis of 23 cases. Niger Quart J Hosp Med 1999; 3(3): 205-208.
- Khaan SA, Mohammed Z, Sharma B, Hasan AS. Tuberculosis of frontal bone. Indian J Tuberc 2001; 48(2): 95-96.
- Sardona K, Koranne RV, Langan U, et al. Ocular Scrofuloderma with unilateral proptosis. J Dermatol 2002; 29(4): 232-234.
- Okwara A, Whalen C, Byekaso F, et al. Randomized trial of thiacetazone and rifampicin-containing regimens for pulmonary tuberculosis in HIV-infected Ugandans. Makere University-Case Western Reserve University Research Collaboration. Lancet 1994; 344: 1323-1328.
- Jones BE, Otaya M, Antoniskis D, et al. A prospective evaluation of antituberculosis therapy in patients with human immunodeficiency virus infection. Am J Respir Crit Care Med 1994; 150: 1499-1502.
- 29. Farmer P. DOTS and DOTS-Plus: not the only answer. Ann NYAcad Sci 2001; 953: 165-184.
- 30. Cohn DL, Catlin BJ, Peterson KL, *et al.* A 62-dose, 6-month therapy for pulmonary and extrapulmonary tuberculosis: a twice weekly, directly observed, and cost effective regimen. Ann Intern Med 1990; 112: 407-415.
- Jasmer RM, Saukkonen JJ, Blumberg HM, et al. Short course rifampin and pyrazinamide for tuberculosis infection (SCRIPT) Study Investigators. Ann Intern Med 2002; 137: 640-647.
- Chaulk CP, Kazandjion VA. Directly observed therapy for treatment completion of tuberculosis: census treatment of the public health Tuberculosis Guidelines panel. JAMA 1998; 279: 943-948.

- 33. Federal Ministry of Health (Nigeria). National Tuberculosis and Leprosy Control Programme: Revised Workers Manual. Fed Min Health. Department of Primary Health Care and Disease Control. (Edited by: Orjioke C J, Sofola T O (Mrs), Chitimba N, et al.), 3rd Edn. Jos: FAB Anieh Printers. 1997: 1-202.
- 34. Baltussen R, Floyd K, Dye C. Cost effectiveness analysis of strategies for tuberculosis control in developing countries. BMJ 2005; 33: 1364-1377.
- 35. Chaisson RE, Clermont HC, Holt EA, et al. JHU-CDS Research Team. Six-months supervised intermittent tuberculosis therapy in Haitian patients with and with out HIV infection. Am J Respir Crit Care Med 1996; 154: 1034-1038.
- Fodor T, Pataki G, Schrettner M. PAS infusion in treatment of multidrug-resistant tuberculosis [Letter]. Int J Tuberc Lung Dis 2000; 4: 187-188.
- Mitcison D A, Nunn A J. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. Am Rev Respir Dis 1986; 133: 423-430.
- Hawken M, Nunn P, Gathua S, et al. Increased recurrence of tuberculosis in HIV-1-infected patients in Kenya. Lancet 1993; 342: 332-338.
- Egah DZ, Banwat EB, Alanana JA, et al. Tuberculosis in Jos, Nigeria: A-nine year review of laboratory report at the Jos University Teaching Hospital. Niger Med Practi 2004; 46(2): 33-35
- 40. Peters EJ, Ekott JU, Eshiet GA, Ayonechi CC. Tuberculosis in Calabar: a ten year review (1994-2003). Nig J Med 2005; 14(4): 381-385.
- Cummings KC, Mohle-Boetani J, Royce S, Chris DP. Movement of tuberculosis patients and the failure of complete tuberculosis treatment. Am J Respir Crit Care Med 1998; 157(4):1249-1252.
- 42. Chaisson RE, Clermont HC, Holt EA, et al. JHU-CDS Research Team. Six-months supervised intermittent tuberculosis therapy in Haitian patients with and with out HIV infection. Am J Respir Crit Care Med 1996; 154: 1034-1038.
- 43. Allaud D, Kalkut GE, Moss AR, *et al.* Transmission of tuberculosis in New York city-An analysis of DNA fingerprinting and conventional epidemiological methods. N Engl J Med 1994; 330: 1710-1716.
- Coronado VG, Beck-Sague CM, Hutton MD, et al. Transmission of multidrug-resistant Mycobacterium tuberculosis among persons with human immunodeficiency virus infection in an urban hospital: epidemiologic and restriction fragment length polymorphism analysis. J Infect Dis 1993; 168: 1052-1055.

- 45. Netto EM, Dye C, Raviglione MC. Global monitoring and surveillance project progress in global tuberculosis control 1995-1996 with emphasis on 22 high-incidence countries. Int J Tuberc Lung Dis 1999; 3: 310-320.
- Kenyan TA, Nwasekaga MJ, Huebner R, et al. Low levels of drug resistance amidst rapidly increasing tuberculosis and human immunodeficiency virus co-epidemics in Botswana. Int J Tuberc Lung Dis 1999; 3: 4-11.
- 47. Brudney K, Dobkin I. Resurgent tuberculosis in New York city. Human immunodeficiency virus homelessness and the decline of tuberculosis control programmes, Am Rev Respir Dis 1991; 144: 745-749.
- 48. Small P M, Shafer R W, Hopewell P C, et al. Exogenous reinfection with multi-drug-resistant *Mycobacterium tuberculosis* in patients with advanced HIV infection. N Engl J Med 1993; 328: 1137-1144.
- China Tuberculosis control collaboration. Results of directly observed short course chemotherapy in 112642 Chinese patients with smear-positive tuberculosis. Lancet 1996; 347: 358-362.
- Dosumu EA. The role of DOTS and tuberculosis treatment supervisor in enhancing patient compliance with tuberculosis chemotherapy in Nigeria. Niger Med Practi 2004; 45(6): 102-105.
- Ogbonaya LU. A comparative study of home-based lay worker supervised and facility-based health worker supervised Dots in Enugu, Nigeria. Orient J Med 2004; 16(2): 1-6
- 52. Ekweani CN. Anti-tuberculosis chemotherapy: 120 years on. Ann Afri Med 2004; 3(3): 116-119.
- 53. Mekonnen T, Abseno M, Meressa D, Fekde B. Prevalence and management outcomes of anti TB drugs induced hepatotoxicity, St. Peter TB Specialised Hospital. J Ethiopia Med Pract 2002; 4(1): 32-38.
- 54. Monno L, Angarano G, Carbonara S, et al. Emergence of drug resistant *Mycobacterium tuberculoss* in HIV-infected patients. Lancet 1991; 337: 852.
- 55. Herrera D, Cano R, Godoy P, *et al.* Multidrug-resistant tuberculosis outbreak on an HIV ward- Madrid, Spain, 1991-1995. Morb Mortal Wkly Rep 1996; 45: 330-333.
- 56. Mohamoudi A, Iseman MD. Pitfalls in the cure of patents with tuberculosis. JAMA 1993; 270: 65-68.
- 57. Reichman LB. Tuberculosis elimination- what's to stop us? Int J Tuberc Lung Dis 1997; 1: 3-11.