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Is the directly observed therapy short course (DOTS) an effective strategy for tuberculosis control in a developing country?

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PEER REVIEW

Peer reviewer

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Comments

This is an excellent review of a major fulcrum of the world TB control programme. The author has shown that SAT may be as effective as DOT in controlling TB. The resources thus saved from implementing SAT may be used to expand the programme to regions not previously covered.

(Details on Page 230)

ABSTRACT

Objective: To investigate the effectiveness of the directly observed therapy short course (DOTS) strategy in tuberculosis control in developing countries. **Methods:** Secondary data was searched to identify relevant publications. Databases, organizational websites and search engines were utilized. Sort criteria were then applied to further limit the articles used. **Results:** A total of 50 articles were found. Abstracts of the 50 articles were then scrutinized and 26 that met the inclusion criteria were identified. Full length copies of these articles were obtained and analysed to extract salient details which were relevant to the research question. **Conclusions:** DOTS as a whole remains the cornerstone of tuberculosis control in developing countries. In the setting of high human immunodeficiency virus (HIV) infection rates and HIV/tuberculosis co−infection, there is a pressing need to modify DOTS to increase its relevance.

1. Introduction

Tuberculosis is the leading cause of death due to an infectious agent; it is both preventable and treatable[1]. Globally, there are more cases of tuberculosis today than in previous epochs of human history. Tuberculosis and human immunodeficiency virus (HIV) co−infection and increasing multi−drug resistance is greatly responsible for tuberculosis assuming almost epidemic proportions[2−4]. It affects one third of the world's population of well over 6 billion people,

and 8.8 million people develop active disease each year[5]. Globally, tuberculosis causes about 2 million deaths yearly[6,7]. In response to this catastrophe, the World Health Organisation's (WHO) global tuberculosis programme in 1993 declared tuberculosis a global emergency and began promoting a management strategy called directly observed therapy short course (DOTS). By 2005, 187 countries had started implementing DOTS with 4.9 million cases of tuberculosis being treated using DOTS in that year alone[8]. DOTS has 5 key components as identified by WHO[9]:

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• Government commitment to sustained tuberculosis control activities.

• Case detection by sputum smear microscopy among symptomatic patients.

• Standardized treatment regimen of 6 to 8 months for at least all confirmed sputum smear positive cases, with DOTS for at least the initial 2 months.

• A regular, uninterrupted supply of all essential anti–tuberculosis drugs.

• A standardized recording and reporting system that allows assessment of treatment.

Under the DOTS strategy, anti–tuberculosis medications are swallowed by patients under the supervision of a health worker (DOT) thereby ensuring that proper medications are given at proper intervals and at the right doses. Also, DOTS increases the accuracy of diagnosis of tuberculosis by advocating sputum smear microscopy thereby reducing the spread of tuberculosis[9]. Indigent patients are catered for under the DOTS programme as free medications are provided and the duration of illness is reduced. Ultimately, the social stigma associated with DOTS is reduced thereby encouraging symptomatic persons to present for medical care.

The need for a strategy to enhance adherence to anti–tuberculosis chemotherapy is buttressed by recent studies which show that even in industrialized countries and among knowledgeable and educated individuals, at least 30% of patients, owing to a perception of improvement, do not take their medication properly and stop treatment after a while[10].

2. Materials and methods

Secondary data was searched to identify relevant publications. The keywords used were:

• "Directly observed therapy short course" or "DOTS" or "DOT".

• "Tuberculosis control" or "tuberculosis treatment".

• "Developing countries" or "developing nations".

The secondary data was from:

• Databases: this included PubMed, Popline, Global Health and Web of Science.

• Organisational websites: WHO website was used.

• Search engines: Google Scholar and Scirus were used.

Database search for relevant literature was done in February 2013, in two phases.

2.1. Phase 1

Keyword search was done using "or" for synonyms. Search terms were then combined using "and".

2.2. Phase 2

Sort criteria were applied, according to database, to obtain more relevant articles.

3. Results

A total of 50 relevant articles were identified from the phase 1 and 2 processes. PubMed provided 22 articles while Popline, Global Health and Web of Science provided 6, 10 and 6 articles respectively. The organizational website and search engines collectively provided 6 articles. Abstracts of the 50 articles were then scrutinized and 26 that met the inclusion criteria were identified. Full length copies of these articles were then obtained and analysed. The inclusion and exclusion criteria used are stated below.

3.1. Inclusion criteria

• English language: Only articles written in English language were used to avoid translation errors and misinterpretation.

• Peer reviewed vs. non peer reviewed articles: Peer reviewed articles were also preferred because of their authenticity.

• Source of article: Articles from databases such as PubMed, Popline, Global Health, and Web of Science were preferred because they focussed on health issues.

• Literature relevance to research question: Article titles and abstracts were scrutinized to ensure that the contents were related to the research question.

• Publication dates: Publications with dates from 1993 to 2013 were included because DOTS was formally launched in 1993. However, articles published within the last 5 years were preferred because information was more relevant to present day.

3.2. Exclusion criteria

• Language: Articles that were not in English language were excluded.

• Relevance to research question: Journal articles with no relevant information on study were excluded.

• Publication dates: Articles with publication dates before 1993 were excluded.

4. Discussion

Between 1995–2008, 50 million patients with tuberculosis were cured using the DOTS strategy and this averted up to 7 million deaths[10]. China recorded massive success with DOTS as the number of detected tuberculosis patients rose from 835 in 1990 to about 130 000 in 1995; about 91% of those who started treatment in 1993 got cured. Bangladesh has also recorded similar success with DOTS. About 72 000 cases of tuberculosis are reported in Bangladesh every year with DOTS covering 90% of the population and achieving a treatment success rate of 80%[11].

A study by Dosumu supports the use of DOT[12]. This study among 500 Nigerians on DOT was to determine

their compliance to anti–tuberculosis drugs. Total (100%) compliance and cure rate were recorded with the use of DOT and TB home visitor in this study. These results affirm the effectiveness of DOT in enhancing compliance and hence cure of tuberculosis.

A structured review of 27 articles on DOT with treatment completion as the primary outcome was carried out to develop public health guidelines for tuberculosis treatment[13]. This review showed that treatment completion rates were most likely to exceed 90% when treatment was based on a patient–centred approach using DOT.

Similar benefits of DOT were also reported by Steffen and colleagues who compared treatment completion rates of persons using self–administered treatment (SAT) facilities in Rio de Janeiro, Brazil[14]. Treatment completion rates were 71% in SAT facilities and 79% in DOT facilities. They also analysed the patients' costs of TB care and estimated the incremental cost effectiveness ratio (ICER) of DOT per completed treatment. They found that DOT increased the cost for both the patient and health system during the treatment phase. However, the SAT increased costs in the pre–diagnostic phase. In SAT facilities, the costs per completed treatment were US$ 194 for patients and US$ 189 for the health system, compared to US$ 336 and US$ 726 in DOT facilities. The ICER was US$ 6 616 per completed DOT treatment compared to SAT[14].

Another head to head comparison of DOT with SAT was carried out by Moosazade *et al*. in Mazandaran Diseases Control Centre Iran from 2005 to 2010[8]. Of 683 registered patients, 362 were in the DOT group and 321 ones were in the SAT group. The DOT group recorded significantly higher success levels of 92% when compared with 83.2% in the SAT group was 2% less than the WHO target while in the DOTS group, it was 7% more than the WHO target.

In India, the therapeutic efficacy of DOTS and non–DOTS interventions in tuberculosis cure were studied using a randomised trial design by Murali and Udaya[15]. In this study, 306 pulmonary tuberculosis patients randomly allocated to the two study groups, 153 in the DOTS–group and 153 in the non–DOTS group. There was a statistically significant difference in outcome as 91% of the DOTS group and 53% of the non–DOTS group were observed to be smear–negative after 6 months of chemotherapy. The findings pointed to the superiority of DOTS over self–administered regimens in the prognosis of tuberculosis patients[15].

Favorov *et al*. also documented significant success in the tuberculosis control programme in Kazakhstan following implementation of DOTS in 1998[16]. This study compared the tuberculosis mortality rate (MR) and case fatality rate (CFR) in Kazakhstan for 1998–2003 to those of Uzbekistan and four adjacent Russian Federation states that had not introduced DOTS. The MR from tuberculosis in Kazakhstan decreased markedly, but remained stable or increased in neighbouring territories. Similarly, Kazakhstan recorded a marked decrease in CFRs while Uzbekistan showed a marginal decrease; these rates increased in other neighbouring regions. DOTS appeared to have helped avert approximately 17 800 deaths in Kazakhstan from 1998 to 2004. The deaths averted were considered to be an indicator of DOTS effectiveness.

The main criticism of DOTS derives from analysis of its direct observation component. In order to produce the desired results, DOT requires efficient and adequately staffed health services which may not be available in high burden and resource poor countries[17]. The cost of providing DOT is also high and it is time consuming for both the patients and caregivers[14]. Researchers have also questioned the appropriateness of DOT in areas with high burden of HIV that utilize SAT for highly active antiretroviral therapy (HAART). When compared with SAT, DOTS has not demonstrated consistent superiority with regards to cure or treatment completion rates. Ethical issues arising from lack of privacy and stigmatization during DOT have also been highlighted as a drawback[18].

Some studies comparing DOT with SAT have produced interesting results. A Cochrane review of 11 trials with 55 609 participants showed no statistically significant difference between DOT and SAT in terms of cure (RR 1.02, 95% *CI* 0.86 to 1.2) or treatment completion in people receiving treatment for tuberculosis[19]. These findings are further supported by Walley *et al*. who studied 497 adults in Pakistan with tuberculosis[20]. These patients were assigned to one of three groups namely DOT with direct observation of treatment by health workers, DOT with direct observation of treatment by family members and SAT. The main outcome measures were cure, and cure or treatment completion. None of the three strategies tested was shown to be superior to the others, and cure rates did not improve with DOT. Walley *et al*. concluded that the effectiveness of direct observation of treatment remains unclear, and further operational research is needed[20].

A novel testing of the efficiency and feasibility of SAT was done by Nackers *et al*. in Kenya in 2011. They assessed adherence to standard anti tuberculosis chemotherapy with fixed dose combinations using SAT among tuberculosis patients. Adherence was tested at home with urine testing for isoniazid, pill count, interviewer–administered questionnaire and visual analogue scale (VAS). Of the 212 patients studied, 95.2% of them reported not having missed a tablet in the last 4 days. On the VAS, complete adherence was estimated at 92.5% while isoniazid urine test was positive for 97.6% of the patients. Pill count could be assessed among only 70% of the interviewed patients. Among them, it was complete for 82.3%. Overall, 193 (91.0%) were successfully treated (cured or treatment completed) lending credence to the efficiency of SAT[21].

A systematic review in 2012 by Azhar studied recurrence of TB after its successful treatment with standard short course chemotherapy under DOTS guidelines in India[22]. Seven studies were included in this review after applying the inclusion, exclusion and quality assessment criteria. Azhar found high relapse rates (almost 10%) in almost all the studies from India. Retreatment cases accounted for about 24% of all TB cases. This review highlighted the findings of Volmink and Garner that DOT is not recommended for re–treatment patients, as re–treatment patients assigned to DOT group in the systematic review had a worse treatment outcome than those in the SAT group[19]. However, Azhar

concluded that the sample size of Volmink's study was too small to be conclusive.

Another systematic review by Cox *et al.* in 2008 assessed the ability of standard DOTS therapy to result in lasting cure for patients treated under routine programmatic conditions[23]. A total of 16 studies met the inclusion criteria; ten of them were controlled clinical trials and six were either studies done under programmatic conditions or observational studies from functioning tuberculosis programmes. Levels of disease recurrence after successful treatment ranged from 0% in a small controlled clinical trial in Singapore to 14% among miners in South Africa. High rates of recurrence were also seen in the observational studies carried out within DOTS programmes in India[23].

Literatures from other African studies also support this position. Sanneh and Pollock did a quantitative cross sectional study of tuberculosis patients in the western division of Gambia[24]. They compared patients treated before introduction of DOT with those treated using DOT. There was no statistically significant difference between the treatment outcomes of the two medication policies. Another study from Africa by Zwarsenstein *et al.* reported very unique findings[25]. This was a randomized controlled trial involving newly diagnosed and retreatment cases of tuberculosis who were randomized into two groups for therapy: DOT and self–supervision. Self–supervised patients had more successful treatment outcomes when compared with DOT patients (difference between groups 6%). Also, retreatment patients who were self–supervised had significantly more successful treatment outcomes when compared to those on DOT [difference between groups 32% (11%–52%)].

A major factor that has adversely affected DOTS is multidrug resistant tuberculosis (MDR TB) which is linked to the global HIV epidemic. This refers to resistance to rifampicin and isoniazid which are the most effective anti–tuberculosis drugs[11]. In response to the threat posed by MDR TB, WHO with its partner agencies launched the DOTS–PLUS strategy in 1999 to replace DOTS. DOTS–PLUS is based on the same guiding principles as DOTS. However, DOTS–PLUS advocates the use of sputum cultures and drug susceptibility tests for diagnosis with use of second line as well as first line drugs for treatment[2]. The need for this paradigm shift was reiterated by Dauda who studied 1 692 tuberculosis patients treated with DOTS; of these 650 (38.4%) had HIV/tuberculosis co–infection [26]. Only 40% of the patients were cured by DOTS falling short of the WHO target of 85% cure. Dauda concluded by advocating for new regimens and administration protocols for tuberculosis.

From the foregoing, it is clear that tuberculosis constitutes a grave public health issue which requires an efficient control strategy. It remains an incontrovertible fact that DOTS has significantly mitigated the global effect of tuberculosis, but it has its inherent weaknesses. The most criticized component of DOTS has been supervised treatment of tuberculosis patients (DOT). However, in spite of concerns about its effectiveness, DOTS as a whole will remain the cornerstone of tuberculosis control in developing countries and indeed globally. The high cost of implementing DOT by health workers at health facilities and the huge manpower requirements are areas which require urgent revision especially in low–middle income countries. DOT by community volunteers and family members may provide a solution to these challenges. It can address the lack of capacity to administer DOTS through health care workers while providing equivalent services at a much reduced cost. This may be a good way of utilizing available resources without compromising the quality of tuberculosis care. In the setting of high HIV infection rates and HIV/tuberculosis co–infection, there is a pressing need to modify DOTS to make it more relevant. This has been achieved by introducing more accurate diagnostic methods and more efficacious drugs into the DOTS–PLUS strategy. However, the use of SAT for HIV/tuberculosis co–infected persons who are also receiving HAART is an interesting innovation that requires further exploration.

Conflict of interest statement

I declare that I have no conflict of interest.

Acknowledgements

Comments

Background
This study has highlighted the threat tuberculosis (TB) has posed from the earliest times to the present as well as the resurgence of this disease due to a large extent by the HIV epidemic. WHO recommends the directly observed treatment short–course treatment (DOTS) strategy for the management of TB. The impact of the disease is largely felt in regions of the world where resources such as finance, manpower, logistics, and technical support available for the management of this condition may be lacking.

Research frontiers
This review examined 26 article relevant to the implementation of DOTS and compared the successes of DOT with that of SAT.

Related reports
A study by Dosumu demonstrated a 100% compliance and cure rate using DOTS. This high success rate was also observed by Chaulk in a systematic review of the effectiveness of DOT using 27 articles. Similar benefits of DOT were also reported by Steffen *et al.* who compared treatment completion rates of persons using SAT facilities in Rio de Janeiro. However the study demonstrated a significantly higher cost in DOTS. Other studies from developing countries

such as Iran (Moosazade *et al.*) and India (Murali *et al.*) have shown the superiority of DOT over SAT. However, the high cost of DOT vis a vis manpower, technical support, logistics and transportation, may reduce its efficacy in developing countries.

Innovations & breakthroughs

SAT has been shown to be equivalent to DOT by some authors. The relatively lower cost of implementing SAT and the fact that it may overcome some of the inherent deficiencies of DOT such as patient cost and stigmatization makes it a promising option in areas with a high TB burden especially HIV/TB co–infected patients.

Applications

This paper has made a strong case for SAT in resource poor and high TB burden countries, for a rethink of the DOTS strategy and the evaluation and workability of less expensive strategies such as the SAT.

Peer review

This is an excellent paper of a major fulcrum of the world TB control programme. The author has shown that SAT may be as effective as DOT in controlling TB. The resources thus saved from implementing SAT may be used to expand the programme to regions not previously covered.

References

[1] Raviglione M, Marais B, Floyd K, Lönnroth K, Getahun H, Migliori GB. Scaling up interventions to achieve global tuberculosis control: progress and new developments. *Lancet* 2012; **379**(9829): 1902–1913.

[2] Baltussen R, Floyd K, Dye C. Cost effectiveness analysis of strategies for tuberculosis control in developing countries. *Brit Med J* 2005; **331**(7529): 1364.

[3] Huldah I. Nwokeukwu HI, Okafor PN, Okorie O, Ukpabi IK. Paediatric multidrug–resistant tuberculosis with HIV coinfection: A case report. *Case Rep Med* 2013; doi: 10.1155/2013/756152.

[4] Philips L. Infectious disease: TB's revenge. *Nature* 2013; **493**: 14–16.

[5] Osborne R. First novel anti–tuberculosis drug in 40 years. *Nature Biotechnol* 2013; **31**: 89–91.

[6] World Health Organisation. The global plan to stop tuberculosis 2011–2015: transforming the fight towards elimination of tuberculosis[R]. Geneva: WHO, 2010.

[7] World Health Organization. Global tuberculosis control: a short update to the 2009 report. Geneva: WHO 2009. [Online] Available from: http:// www.who.int/ tb/publications/global_report/2009/ update/tbu_9.pdf.[Acccessed on 21st November 2012]

[8] Moosazade M, Jamshidi M, Amiresmaili M, Nezammahalleh A. A comparison of directly observed therapy and self–administered therapy strategies in treatment of pulmonary tuberculosis: A cohort study in north of Iran. *Middle–East J Sci Res* 2012; **11**(7): 873–880.

[9] Tumbo JM, Ogunbanjo GA. Evaluation of directly observed treatment for tuberculosis in the Bojanala health district, north west province of South Africa. *Afr J Prim Health Care Family Med* 2011; **3**(1): doi: 10.4102/phcfm.v3i1.191.

[10] Marais BJ. History of tuberculosis and drug resistance. *New Engl J Med* 2013; **368**(1); 88–90.

[11] Ahmad N. Stop TB strategy–DOTS. *Int J Student Res* 2011; **1**(1): 16–18.

[12] Dosumu E. Compliance in pulmonary tuberculosis patients using directly observed treatment short course. *Afr J Med Sci* 2001; **30**(1–2): 111–114.

[13] Chaulk CP, Kazandjian VA. Directly observed therapy for treatment completion of pulmonary tuberculosis – Consensus statement of the public health tuberculosis guidelines panel. *J Am Med Assoc* 1998; **275**(12): 943–948.

[14] Steffen R, Menzies D, Oxlade O, Pinto M, de Castro AZ, Monteiro P. Patients' costs and cost–effectiveness of tuberculosis treatment in DOTS and non–DOTS facilities in Rio de Janeiro, Brazil. *PLoS ONE* 2010; **5**(11): e14014.

[15] Murali MS, Udaya KN. A comparative study of dots and non–dots interventions in tuberculosis cure. *Indian J Commu Med* 2004; **29**(1): 18–19.

[16] Favorov M, Belilovsky E, Aitmagambetova I, Ismailov S, White M, Chorba T. Tuberculosis deaths averted by the implementation of the DOTS strategy in Kazakhstan. *Int J Tuberc Lung Dis* 2010; **14**(12): 1582–1588.

[17] Fochsen G, Deshpande K, Ringsberg KC, Thorson A. Conflicting accountabilities: Doctor's dilemma in TB control in rural India. *Health Policy* 2009; **89**: 160–167.

[18] Selgelid MJ, Reichman LB. Ethical issues in tuberculosis diagnosis and treatment. *Int J Tuberc Lung Dis* 2011; **15**(Suppl 2): S9–S13.

[19] Volmink J, Garner P. Directly observed therapy for treating tuberculosis. *Cochrane Database Syst Rev* 2007; **4**: CD003343.

[20] Walley JD, Khan A, Newell J, Khan M. Effectiveness of the direct observation component of DOTS for tuberculosis: a randomised controlled trial in Pakistan. *Lancet* 2001; **357**(9257): 664–669.

[21] Nackers F, Huerga H, Espié E, Aloo AO, Bastard M, Etard J, et al. Adherence to self–administered tuberculosis treatment in a high HIV–prevalence setting: A cross–sectional survey in Homa Bay, Kenya. *PLoS ONE* 2012; **7**(3): e32140.

[22] Azhar GS. DOTS for TB relapse in India: A systematic review. *Lung India* 2012; **29**(2): 147–153.

[23] Cox HS, Morrow M, Deutschmann PW. Long term efficacy of DOTS regimens for tuberculosis: systematic review. *Brit Med J* 2008; **336**: 484–487.

[24] Sanneh AF, Pollock J. Comparison of pulmonary TB DOTS clinic medication before and after the introduction of daily DOTS treatment and attitudes of treatment defaulters in the Western Division of the Gambia. *Afr Health Sci* 2010; **10**(2): 165–171.

[25] Zwarenstein M, Schoeman J, Vundule C, Lombard C, Tatley M. Randomised controlled trial of self–supervised and directly observed treatment of tuberculosis. *Lancet* 1998; **352**(9137): 1340–1343.

[26] Dauda M. Evaluation of the efficacy of directly observed treatment short course (DOTS) in patients with tuberculosis and HIV Co–infection in Kano, Nigeria. *Rev Infect* 2010; **1**: 218–223.