

## DOT or not? Direct observation of anti-tuberculosis treatment and patient outcomes, Kerala State, India

V. N. Balasubramanian,\* K. Oommen,\* R. Samuel†

\*District Tuberculosis Centre, Pathanamthitta District, Kerala, †Department of Community Health, Christian Medical College, Vellore, India

### SUMMARY

**SETTING:** The Pathanamthitta District of Kerala State, India, where the directly observed treatment, short-course (DOTS) programme was started in October 1994.

**OBJECTIVE:** To determine the frequency with which direct observation actually occurred within a district-level DOTS programme, and the association of treatment observation with treatment outcome under programme conditions.

**DESIGN:** This retrospective study included 200 consecutive, newly-detected, smear-positive patients registered under the project between February 1995 and February 1996 at the District Tuberculosis Centre, as well as health workers responsible for providing directly observed treatment (DOT) who were separately and confidentially interviewed. Treatment outcomes were identified from results of sputum smear examinations for acid-fast bacilli.

**RESULTS:** Although all patients were recorded as having received DOT, more than a quarter of patients (26.5%) did not actually receive it. The 53 patients who were not directly observed were much more likely to have treatment failure or relapse, as compared to those who had received DOT (45% vs 3%, relative risk 16.6, 95% confidence intervals 6-46,  $P < 0.001$ ). Women were somewhat less likely than men (61% vs 76%,  $P = 0.06$ ) to receive DOT. Non-receivers of DOT accounted for 86% (24/28) of treatment failures or relapses.

**CONCLUSION:** Patients treated without direct observation have a substantially higher risk of adverse outcome than those treated under direct observation. To be maximally effective, the DOTS programme must be both confidential and convenient.

**KEY WORDS:** tuberculosis; directly observed treatment; DOTS; non-compliance; India

DIRECTLY OBSERVED TREATMENT, short-course (DOTS) was introduced in India in 1993 as part of the Revised National Tuberculosis Control Programme (RNTCP), following a review of India's National Tuberculosis Programme (NTP) a year earlier.<sup>1</sup> The DOTS strategy has five components: political will, diagnosis by microscopy, regular supply of drugs for short-course treatment, direct observation of treatment (DOT), and systematic monitoring.<sup>2</sup> Directly observed treatment, in which a health worker observes and assists as patients take their medicine, is the most controversial component of DOTS.<sup>3-8</sup> In RNTCP districts, the policy is for all patients registered for short-course anti-tuberculosis treatment under the government health care system to receive DOT.<sup>9</sup> We conducted a retrospective study to ascertain whether patients actually received DOT and to determine the association of DOT with treatment outcomes under programme conditions.

### STUDY POPULATION AND METHODS

The RNTCP was started in October 1994 in Pathanamthitta District of Kerala State, India. This district has a population of 1.18 million, in an area of 2642 km<sup>2</sup>. The District Tuberculosis Centre has two tuberculosis units, each with its own supervisory staff. There are 16 microscopy centres. In rural areas, paramedical workers at primary health centres or rural health posts provide DOT. At the time of the study (between February 1995 and February 1996), only health workers were providing DOT.

Treatment under direct observation is given thrice weekly. For new smear-positive patients, intensive phase treatment is given for 2 months (3 months if the sputum smear is positive at 2 months) with isoniazid, rifampicin, pyrazinamide and ethambutol. The policy states that during the intensive phase every dose taken is to be directly observed by a health worker or a

Correspondence to: Dr Reuben Samuel, Medical Officer, Department of Community Health, Christian Medical College, Vellore 632 002, Tamil Nadu, India. Tel: (+91) 416-262 603/903 Ext. 4207. Fax: (+91) 416-262 268. e-mail: reuben\_samuel@hotmail.com

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community volunteer who is not a family member. In the continuation phase, the first dose of treatment every week is to be directly observed, with the remaining two follow-up doses self-administered by the patient.<sup>9</sup> Sputum is examined after 2 and 4 months of treatment, at the end of treatment, and if symptoms develop after stopping treatment. The treatment regimens used are those recommended by the World Health Organization. Patients are considered cured if the results of two sputum smears for acid-fast bacilli (AFB) are negative, one of which is done at the end of treatment. Treatment is considered to have failed if a patient has a positive smear 5 months or more after starting treatment. Relapse is considered to have occurred when a patient who had previously been cured and was sputum smear-negative has a positive smear.<sup>2</sup> A patient who at any time after registration does not take anti-tuberculosis drugs consecutively for 2 months or more, is said to have defaulted.

Although the treatment records of all of the patients indicated that DOT had been provided, some patients did not in fact receive observed treatment, but instead received their treatment regimen for self-administration. Generally, health workers handed medicines for the full course of drugs for one week or one month to the patient with strict instructions to take the medicines; the health worker then enquired on a weekly or monthly basis about the patient's progress. Health workers admitted to recording 'observed' on the treatment card even when observation had not been done. Follow-up sputum examinations were conducted as per schedule.

Of the patients registered during the study period, 15 had died and 13 were lost to follow-up and hence were not available for interview. No patient had been transferred. Interviews were conducted at the patient's residence or at the District Tuberculosis Centre when patients reported for follow-up sputum smear examination. One of the authors or a trained interviewer conducted structured, confidential interviews of 200 consecutive newly-detected smear-positive patients registered during the study period. All patients were reported to have taken the full course of treatment. The health workers responsible for administering DOT to these patients were also interviewed using a separate questionnaire, after being reassured that they would not face censure if they admitted that DOT had not been provided according to policy. There was no reference to treatment outcome in the interviews. From these interviews, it was determined whether patients had actually received DOT. In case of disagreement between the patients and health workers regarding administration of DOT, the patient's statement was considered as correct. If DOT had not been given, the reasons were enquired into.

## RESULTS

Of the 200 patients interviewed, 70% were rubber tappers or daily wage-earning manual labourers. Of these, only 147 (74%, of whom 85% were men and 15% were women) patients had actually received DOT. Among the 53 (27%) patients who did not receive DOT, 74% were men and 26% were women. The mean age of those who did and those who did not receive DOT was 46.5 vs 47.4 years ( $P = \text{NS}$ ). In each tuberculosis unit, similar numbers of patients had been registered and there was no significant difference in the proportion of patients receiving and not receiving DOT (80/102, 78% vs 67/98, 68%,  $P = 0.1$ ). Multiple regression analysis showed that neither age, sex nor tuberculosis unit were associated with non-receipt of DOT.

The reasons most commonly cited by the 53 (27%) patients who did not receive observed treatment were age/infirmity ( $n = 15$ , 28%), and social stigma ( $n = 15$ , 28%) (see Table). Social stigma was cited as the reason for not receiving DOT much more commonly by women than by men (7/14, 50% vs 8/39, 21%,  $P = 0.04$ ).

There were large and significant differences in the cure, failure and relapse rates between patients who did and did not receive DOT (Table). Of those who did not receive DOT, 26% had treatment failure and 19% had relapse, while among those who did receive DOT less than 3% had relapse or failure (24/53, 46% vs 4/147, 3%, relative risk 16.6; 95% confidence intervals 6–46,  $P < 0.001$ ). Of those with available smear results, patients who did not receive DOT had a higher proportion of positive sputum smears after 2 months of treatment (15/50, 30% vs 14/138, 10%,  $P < 0.001$ ). Patients who did not receive DOT and who had positive sputum smears after 2 months of treatment were more likely to have treatment failure or relapse than were patients who did receive DOT and who had positive smears after 2 months of treatment (11/15 vs 1/14,  $P = 0.001$ ).

Among patients who did not receive DOT, the risk of failure or relapse was elevated in all age groups, among both males and females, at both tuberculosis units, and regardless of the reason given for not participating in treatment observation. Patients who had conflict with the health worker or who refused treatment had even higher rates of treatment failure and relapse (see Table). Of the 28 patients who had treatment failure or relapse in this series, those who had not taken DOT accounted for 86% (24/28).

## DISCUSSION

We found that a substantial proportion of patients in a DOTS programme—more than a quarter—did not actually receive treatment under observation. Advanced age/infirmity and fear of social stigma were the pri-

**Table** Outcomes of patients who did and did not receive directly observed treatment (DOT), Kerala State, 1995–1996

Variable	n (%)	Cure (%)	Failure (%)	Relapse (%)	RR of failure or relapse	95%CI	P value
DOT							
Received DOT	147 (73.5)	97.3	2.0	0.7	1.0	—	<0.001
Did not receive DOT	53 (26.5)	54.7	26.4	18.9	16.6	6–46	
Among patients not receiving DOT							
Sex							
Female	14 (26.4)	57.1	21.4	21.4	1.0	—	0.8
Male	39 (73.6)	53.8	28.2	17.9	1.1	0.5–2.2	
Age (years)							
>48	28 (52.8)	57.1	32.1	10.7	1.0	—	0.7
≤48	25 (47.2)	52.0	20.0	28.0	1.1	0.6–2.0	
Treatment unit							
TB Unit B	31 (58.5)	58.1	19.4	22.6	1.0	—	0.6
TB Unit A	22 (41.5)	50.0	36.4	13.6	1.2	0.7–2.2	
Reason given for not receiving DOT							
Age/infirmity	15 (28.3)	60.0	33.3	6.7	1.0	—	0.1
Social stigma	15 (28.3)	53.3	20.0	26.7	1.2	0.5–2.7	0.7
Conflict with health worker/refusal	7 (13.2)	0	42.9	57.1	2.5	1.4–4.7	0.009
Financial difficulties	5 (9.4)	80.0	20.0	0	0.5	0.1–3.2	0.6
Distance/inconvenience	5 (9.4)	80.0	0	20.0	0.5	0.1–3.2	0.6
Trusted by health worker	4 (7.5)	50	50	0	1.3	0.4–4.0	0.7
No reason given	2 (3.8)	100	0	0	undefined	—	0.3

RR = relative risk; CI = confidence interval.

mary reasons given for not participating in DOT. Patients not receiving DOT were strikingly more likely to have treatment failure or relapse, and accounted for 86% (24/28) of patients with these unfavourable outcomes. In this series, 55% of patients were successfully treated without DOT; this proportion is similar to that observed by others.<sup>10–12</sup> In this study, as in other clinical trials<sup>13–15</sup> and well functioning DOTS programmes,<sup>16</sup> more than 90–95% of patients who actually received DOT had relapse-free cure.

Among smear-positive patients diagnosed, males outnumbered females by a ratio of more than three to one. The finding that women were less likely to participate in DOT, and that social stigma was the most common reason for non-participation among women, suggests that there may be lack of access to DOTS for women. This may be due to the programme's perceived lack of confidentiality and fear of social stigma and rejection.

This study has several limitations. First, since it was retrospective, both workers and patients may have been more likely to admit to non-adherence with DOT in case of treatment failure or relapse. Second, interviewers were not blinded to treatment outcomes, and hence there could have been interviewer bias in the determination of which patients actually received DOT. Third, some patients may have stopped participating in DOT if their symptoms did not improve because they were infected with drug-resistant bacteria. In other words, treatment failure could have caused, rather than resulted from, non-participation in DOT; we cannot prove that if DOT had been given to the patients who had treatment failure or relapse, they would have had more favourable outcomes.

However, our inability to interview patients who had died or were lost to follow-up, and our use of only passive identification of patients with relapse, would tend to *reduce* the association between non-participation in DOT and unfavourable treatment outcomes. The magnitude of the difference in outcomes, and the consistency of these differences in different groups, suggest that our overall findings are valid. Our findings indicate that under field conditions in our programme, direct observation of treatment was associated with an increase in treatment success from 55% to more than 95%. Other than DOT, all diagnostic and treatment practices were similar for patients who did and those who did not receive DOT.

It is important to provide DOT at a time and place that is convenient and acceptable to patients. It has recently been documented that ineffective implementation of DOT can result in no increase, or actually a decrease, in treatment success.<sup>12</sup> Trained midwives,<sup>17</sup> community volunteers,<sup>18</sup> shopkeepers,<sup>18</sup> members of non-governmental organizations,<sup>19</sup> religious leaders,<sup>20</sup> students,<sup>21</sup> cured patients and others can provide DOT. Some very ill patients may benefit from hospitalization.<sup>22</sup> For the few patients for whom none of these options is viable, non-participation in DOT should be noted. The possibility of giving alternative regimens which reduce the risk of development of multidrug resistance (e.g., a treatment regimen that does not contain rifampicin) should be explored, combined with intensive monitoring for treatment failure and relapse.

The findings of this evaluation were used locally to improve programme implementation. For health workers and patients, the importance of participating

in DOT—as documented by these data—was emphasised. As DOT was clearly associated with improved treatment outcomes, the programme identified community volunteers and others who could provide DOT at more convenient and confidential locations so that all patients have the best possible chance of cure. To be maximally effective, the DOTS programme must be both confidential and convenient.

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#### RÉSUMÉ

**CADRE :** Le District de Pathanamthittha dans l'Etat de Kerala en Inde où un programme de traitement directement observé et de courte durée (DOTS) a démarré en octobre 1994.

**OBJECTIF :** Déterminer la fréquence à laquelle l'observation directe a été effectivement réalisée au sein d'un programme DOTS au niveau du district, ainsi que les relations entre le traitement directement observé (DOT) et les résultats obtenus dans des conditions de programme.

**SCHEMA :** Cette étude rétrospective a porté sur 200 cas consécutifs de tuberculose à bacilloscopie positive, récemment détectés, enregistrés dans le projet entre février 1995 et février 1996 au Centre de Tuberculose du District. D'autre part, les travailleurs de santé responsables de l'administration du DOT ont été interviewés séparément et confidentiellement. Les résultats du traitement ont été identifiés à partir des résultats de la bacilloscopie des frottis d'expectoration.

**RÉSULTATS :** Bien que tous les patients aient été enregistrés comme ayant bénéficié du DOT, plus d'un quart d'entre eux (26,5%) ne l'ont pas reçu effectivement. Chez les 53 patients qui n'ont pas bénéficié d'une observation directe, les échecs de traitement et les rechutes ont été beaucoup plus fréquents que chez ceux qui avaient reçu le DOT (45% vs 3% ; risque relatif 16,6 ; intervalle de confiance 95% 6–46 ;  $P < 0,001$ ). Chez les femmes, l'administration effective du DOT a été quelque peu moins probable que chez les hommes (61% vs 76% ;  $P = 0,06$ ). Les sujets ne bénéficiant pas du DOT ont représenté 86% (24/28) des échecs de traitement ou des rechutes.

**CONCLUSION :** Les patients dont le traitement ne comporte pas une observation directe ont un risque substantiellement plus élevé de résultats défavorables que ceux traités sous observation directe. Pour atteindre une efficacité maximale, le programme DOTS doit être à la fois confidentiel et commode.

## RESUMEN

**MARCO DE REFERENCIA:** El Distrito de Pathanamthitha en el Estado de Kerale, India, donde el programa de Tratamiento Directamente Observado, de Corta Duración (DOTS), se inició en octubre de 1994.

**OBJETIVO:** Determinar la frecuencia con la cual se produjo la observación directa en un programa DOTS a nivel distrital, y la asociación del tratamiento directamente observado (DOT) con los resultados del mismo en condiciones de programa.

**MÉTODO:** Este estudio retrospectivo incluyó a 200 pacientes nuevos, con esputo positivo registrados en el proyecto entre febrero de 1995 y febrero de 1996 en el Centro Distrital de Tuberculosis, así como a los trabajadores de la salud responsables en proveer el DOT, que fueron entrevistados en forma separada y confidencial. Los resultados del tratamiento se identificaron a partir de los resultados del esputo para bacilos ácido-alcohol resistentes.

**RESULTADOS:** Aunque todos los pacientes figuraban como habiendo recibido DOT, más de un cuarto de los pacientes (26,5%) en realidad no lo recibieron. Los 53 pacientes que no fueron directamente observados tuvieron con más frecuencia fracasos o recaídas, comparados con quienes recibieron DOT (45% vs 3%, riesgo relativo 16,6, 95% intervalo de confianza 6-46,  $P < 0,001$ ). Las mujeres recibían con menos frecuencia el DOT que los hombres (61% vs 76%,  $P = 0,06$ ). Los que no recibían DOT tuvieron el 86% (24/28) de fracasos de tratamiento o recaídas.

**CONCLUSIÓN:** Los pacientes sin observación directa tienen un mayor riesgo de un resultado adverso que aquellos tratados con observación directa. Para ser bien efectivo el programa DOTS debe ser confidencial y adecuado.