Frequent return as a novel strategy for tuberculosis treatment adherence

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Keywords
Tuberculosis. National health programs. Patient acceptance of health care. Patient Dropouts. Treatment refusal. Directly observed therapy.

Abstract

Objective
Treatment dropout is one of the major obstacles to the control of tuberculosis. The aim of the present study was to evaluate the frequent return strategy instituted at the Ubatuba Tuberculosis Control Program, as well as the program as a whole, identifying and quantifying potential risk factors for dropout.
Methods
The present study was conducted in Ubatuba, Southeastern Brazil. All patients (n=244) notified by the Tuberculosis Control Program in the two years preceding and the two years following the introduction of the frequent return strategy in 1999 were included. We carried out a descriptive analysis of the data and analyzed treatment results and program evaluation indicators. We performed univariate and multivariate analysis in order to identify potential risk factors associated with dropout. We also analyzed the frequent return strategy using chi-squared tests.
Results
The strategy reduced the risk of treatment dropout from 12.3% to 4.9%. Risk factors associated with dropout were lack of schooling (OR=3.01; p=0.051), unemployment (OR=3.36; p=0.046), and alcohol dependence (OR=3.56; p=0.014).
Conclusions
The frequent return strategy reduced the risk of treatment dropout, although results did not reach statistical significance due to the small number of dropouts. This strategy may be an alternative for the supervised treatment for all patients recommended by the World Health Organization.

INTRODUCTION

Patient adherence to tuberculosis treatment is considered as being the greatest impediment to the control and elimination of this disease in the field of Public Health. Lack of adherence is a challenge in terms of the treatment of individual patients, and the development of resistant bacterial strains is also an issue.[11]

In 1994, the World Health Organization (WHO), by means of the 'Global Project on Anti-Tuberculosis Drug Resistance,' showed that resistance is increased in settings where irregularity of treatment is associated with precarious healthcare systems and inefficient tuberculosis programs. [10,13,14]

In 1997, WHO began to recommend the DOTS strategy (Directly Observed Treatment - Short course) for the control of tuberculosis, as an attempt to reduce mortality, morbidity, and disease transmission. One of the aims of this strategy is to ensure the correct use of drugs, thus preventing the emergence of resistant strains. It consists in administering the standardized short treatment scheme under the direct supervision of an observer, at least during the initial stages of

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treatment, and to at least those cases with positive bacterioscopy (sources of infection).[12]

In Brazil, the DOTS strategy has been implemented in a number of healthcare facilities in the last years. However, due to problems inherent to the current healthcare system – which include the sparseness of human and financial resources – operational difficulties prevent this model from being employed for the majority of patients under treatment for tuberculosis.

Ubatuba, a municipality in Southeastern Brazil, showed high rates of tuberculosis treatment dropout (15% to 30% between 1992 and 1996). As an attempt to reduce these rates, a strategy called 'frequent returns' was introduced in the only facility providing care for tuberculosis patients. This strategy consists in reducing the time between medical appointments, especially during the early stages of treatment. Patients are required to visit the health center on a weekly basis during the first month of treatment, every 15 days during the second month, and on a monthly basis from the third month until the end of treatment.

The present study was aimed at evaluating whether the frequent return strategy has been successful in reducing dropout rates in the Tuberculosis Control Program (TCP). In addition, the Program itself was evaluated, and potential risk factors associated with treatment dropout were identified and quantified.

METHODS

A study was conducted including all tuberculosis patients from the municipality of Ubatuba registered between February 1997 and January 2001. The frequent return strategy was introduced in the Program in February 1999. We analyzed the potential outcomes of treatment: discharge following cure, dropout, death due to tuberculosis or other cause, transfer, and change of diagnosis. Treatment dropout occurs when the patient does not show up to the healthcare facility in the 30 days following the scheduled return appointment and cannot be found either by aerogram or home visit. This scenario also assumes that the patient has remained without treatment for 30 consecutive days. Patients whose transfer to other municipalities was not confirmed by the facility to which he or she was referred were also considered as dropouts. Discharge due to transfer was always confirmed by telephone. Hospital admission did not change the patient's status as a Program case, and, regardless of the duration, place, and number of hospital admissions, the result of the treatment was considered. The information and definitions of case and dropout are based on the computing system developed by the Division of Tuberculosis and Other Pneumopathies of the Epidemiological Surveillance Center of the Sao Paulo State Secretariat of Health (EPI-TB, CVE/SP).

We carried out descriptive analyses of all patients included in the study. We excluded confirmed transfers and changes of diagnosis from the evaluation of treatment outcome; these cases were either considered as cases from other municipalities, or were not regarded as cases of tuberculosis, respectively. A number of indicators for program evaluation were constructed according to Ministry of Health technical norms,[7] so as to better reflect the organization of the Program. We also constructed other indicators for evaluating the percentage of diagnosis changes and hospitalizations for clinical and social reasons.

The information for these indicators was obtained by dividing the study into four one-year periods, beginning in February and ending in January of the next year (Year 1, 2, 3, and 4). The indicators were constructed with the aim of evaluating the Program

Table 1 - General characteristics of patients included in the Tuberculosis Control Program. Ubatuba, Brazil, 1997-2001.

Variables	N (N=224)	%
Age group (years)		
0 to 19	16	7.1
20 to 29	48	21.4
30 to 39	65	29.0
40 to 49	50	22.3
50 or more	45	20.1
Gender		
Male	151	67.4
Female	73	32.6
Schooling (complete years)		
None	27	12.1
1 to 3	21	9.4
4 to 7	117	52.2
8 or more	33	14.7
Ignored	26	11.6
Occupation		
Unemployed	17	7.6
Retired	6	2.7
Housewife	16	7.1
Paid work	155	69.2
Others	30	13.4
Previous treatment		
None or does not know	186	83.0
Yes, discharge after cure	24	10.7
Yes, dropout	14	6.3
Clinical classification		
Pulmonary	192	85.7
Pulmonary + extra-pulmonary	16	7.1
Extra-pulmonary	16	7.1
Diagnostic criterion		
Positive sputum bacterioscopy	145	64.7
Positive culture	11	4.9
Histopathology	2	0.9
Other	66	29.5
Associated diseases		
AIDS	28	12.5
Diabetes	5	2.2
Alcoholism	31	13.8
Mental disease	5	2.2
Other	14	6.3
None	141	62.9

Table 2 - Evaluation of treatment results in the Tuberculosis Control Program, according to indicators and year. Ubatuba, Brazil, 1997-2001 (N=211).*

Indicators	Year 1	Year 2	Year 3	Year 4	Linear trend test for proportions
Number of cases	66	39	47	59	
Percentage of discharge after cure	52 (78.8%)	27 (69.3%)	39 (83.0%)	50 (84.7%)	p=0.24
Percentage of deaths due to tuberculosis	6 (9.1%)	1 (2.6%)	1 (2.1%)	1 (1.7%)	p=0.04
Percentage of deaths due to other causes	1 (1.5%)	3 (7.7%)	4 (8.5%)	5 (8.5%)	p=0.10
Percentage of treatment dropout	7 (10.6%)	8 (20.5%)	3 (6.4%)	3 (5.1%)	p=0.13
Percentage of change of diagnosis**	1 (1.5%)	5 (11.4%)	2 (4.1%)	0 (0.0%)	p=0.41

*Excluding changes of diagnosis and confirmed transfers
**Including changes of diagnosis but excluding confirmed transfers (n=219)

and identifying any important changes taken place during the entire period, in addition to allowing for an evolutionary comparison to be made between different years. Results with p-values below 0.05 were considered as statistically significant.

We carried out univariate analysis for the identification of risk factors for dropout, calculating odds ratios and their respective 95% confidence intervals (95% CI). Variables showing p-values below 0.10 were included in the multivariate model. After the identification of these factors, a multivariate model was elaborated for the control of potential confounders by logistic regression, and associations with p-values below 0.05 were considered as statistically significant.

The frequent return strategy was evaluated by comparing dropout rates before and after its introduction. We excluded patients that were unable to receive the intervention, either for having been transferred from other facilities after more than two months of treatment, or for having been admitted to the hospital for more than one month at the beginning of treatment or for more than three months at any time during treatment. These definitions were adopted so as to allow the patients included in the analysis both to receive the intervention and to have the chance to dropout from treatment, if this were the case. The comparison was done using Chi-square tests and odds ratios with 95% confidence intervals. P-values below 0.05 were considered as statistically significant.

Deaths due to tuberculosis and other causes were excluded from univariate and multivariate analyses. In patients with comorbidities, we considered only the first comorbidity of each case.

All analyses were performed using Epi Info version 6.04 and Stata 6.0 software.

RESULTS

In the four years analyzed, 224 patients were treated in the Ubatuba Program. The majority of patients showed the pulmonary form of the disease, diagnosed by sputum bacterioscopy, which was performed in virtually all cases of pulmonary damage. Of the 11 cases diagnosed by culture, eight were diagnosed by

Table 3 - Results of univariate analysis for factors associated with dropout among patients in the Tuberculosis Control Program. Ubatuba, Brazil, 1997-2001.

Variable	N (189)	Dropout(%)	OR	IC 95% OR	p
Gender					0.169
Female	61	4 (6.6)	1		
Male	128	17 (13.3)	2.18	0.67-9.30	
Schooling (years)					0.051
One or more	146	13 (8.9)	1		
None	22	5 (22.8)	3.01	0.74-10.42	
Occupation					0.046
Employed	174	15 (10.3)	1		
Unemployed	15	4 (28.6)	3.36	0.70-12.93	
Prior dropout					0.752
No	177	20 (11.3)	1		
Yes	12	1 (8.3)	0.71	0.01-5.42	
Clinical presentation					0.225
Pulmonary	164	20 (12.2)	1		
Extra-pulmonary and pulmonary + extra-pulmonary	25	1 (4.0)	0.30	0.01-2.07	
Bacterioscopy results among those performed					0.073
Negative	6	7 (19.4)	1		
Positive	135	12 (8.9)	0.40	0.13-1.33	
Associated diseases					0.195
None	123	11 (8.9)	1		
One or more diseases	66	10 (15.1)	1.82	0.65-5.02	
Associated diseases					0.014
None	123	11 (8.9)	1		
Alcoholism	27	7 (25.9)	3.56	1.03-11.43	
Hospital admission					0.379
None	28	16 (12.5)	1		
At least one	61	5 (8.2)	0.62	0.17-1.91	

sputum culture and three by cultures of extra-pulmonary material. The most frequent comorbidities were alcohol dependence and AIDS. Of the seven patients showing more than one associated disease, two had diabetes, and the others showed other non-specified diseases (Table 1).

Treatment outcome in the entire period was as follows: cure, 79.6%; dropout, 10%; death by tuberculosis, 4.3%; death by other causes, 6.2%. AIDS was responsible for 10 of the 13 deaths due to causes other than tuberculosis. There were eight cases of change of diagnosis, five confirmed transfers, and two cases of dropout due to non-confirmed transfer. Of the 14 patients who had previously dropped out from tuberculosis treatment, 11 were discharged after cure, one died of tuberculosis, one died of AIDS, and one was a non-confirmed transfer.

There was a trend towards more patients receiving supervised treatment and HIV testing. None of the patients underwent supervised treatment during the first year of the study and six patients did so in the last year evaluated. In the fourth year, 98% of patients received HIV testing. There was always a high proportion of pulmonary cases among the total tuberculosis cases, and a low proportion of patients without sputum bacterioscopy among all patients with pulmonary damage. There was also a reduction in dropout rates and deaths due to tuberculosis and an increase in cure rates. Deaths due to other causes remained stable throughout the period, and were mostly related to AIDS. Considering the first admission only, there was a slight trend towards an absolute and relative increase in hospital admissions due to clinical reasons, which became more evident in year 4 (p=0.03) (Table 2).

Regarding risk factors for dropout from tuberculosis treatment, patients with zero years of schooling or unemployed were about three times more likely to dropout from treatment. In this analysis, the "schooling" variable was divided into two groups – subjects with no schooling and those with at least one complete year of schooling. Interestingly, there was a protective effect of about 60% for subjects with positive sputum bacterioscopy, when this was performed (p=0.073). Only 8.9% of patients with positive bacterioscopy dropped out from treatment, whereas 19.4% of patients with negative results did so (Table 3).

The presence of a comorbidity increased the chance of dropout by 81%, but this result was not statistically significant. This is probably due to the fact that alcohol dependence accounts for almost 40% of comorbidities. Analyzing alcohol dependence alone, the chance of treatment dropout was about 3.5 times higher in alcoholics than in patients without associated comorbidities (p=0.014) (Table 3).

Variables eligible for inclusion in multivariate analysis were schooling, occupation, associated diseases, and having undergone sputum bacterioscopy. However, only the first three were selected, due to the small number of cases and insufficient number of outcomes (treatment dropout), which prevented us from carrying out multivariate analyses with more than three variables.[3] (Table 4).

In the logistic regression model, alcohol dependence as an associated disease was the only variable whose odds ratios remained stable in the model (p=0.053). The odds ratios for schooling and occupation were greatly reduced, and the associations lost statistical significance (Table 4).

We found a significant reduction in dropout rates and an increase in cure rates among subjects under treatment for tuberculosis. Dropout rates, which, in the first two years were of 12.3%, fell to 4.9% in the third and fourth years. The odds ratio for dropout after February 1999 was 0.36, representing a 64% reduction; however, this result did not reach statistical significance (p=0.084) (Table 5).

DISCUSSION

There was an important reduction in tuberculosis

Table 4 - Results of multivariate analysis for factors associated with dropout among patients in the Tuberculosis Control Program. Ubatuba, Brazil, 1997-2001. (N=189)

Variable	Crude OR	Adjusted OR	95%CI OR	p
Schooling (years)				0.289
One or more	1	1		
None	3.01	2.20	0.51-9.42	
Occupation				0.326
Employed	1	1		
Unemployed	3.36	2.14	0.47-9.82	
Associated diseases				0.053
None	1	1		
Alcoholism	3.56	3.34	0.98-11.36	

Log likelihood =-42.4
p=0.019

Table 5 - Evaluation of the frequent return strategy in a tuberculosis outpatient facility. Ubatuba, Brazil, 1997-2001.

Frequent returns	Dropout (%)	Cure (%)	N	OR	95% CI OR
No (before 02/1999)	10 (12.3)	71 (87.7)	81	1	
Yes (after 02/1999)	4 (4.9)	78 (95.1)	82	0.36	(0.09-1.35)

treatment dropout rates in the municipality of Ubatuba after the introduction of the frequent return strategy, beginning in February 1999. Although this result was not statistically significant, it was important from the viewpoint of public health. However, one of the major limitations of the present study was the small number of total patients (n=224) and dropouts (n=21) seen in the period. Numbers were even smaller in some of the analyses due to exclusions, thereby reducing the power of the study.

Another important limitation of the present study was the fact that some of the information obtained was not standardized. Patients considered to be under risk of abandoning treatment during the frequent return program and submitted to supervised treatment had been identified by means of information that were not included in the tuberculosis notification form. Therefore, information such as correct use of medication and absence from appointments could not be measured. On the other hand, the entire Ubatuba EPI-TB database was checked with the patient files and the tuberculosis notification forms present in the facility, thus ensuring the quality of the data.

According to several authors,[4-6,8] most dropouts occur during the first two to three months of tuberculosis treatment. This indicates the importance of adopting measures capable of reducing dropout rates since the very beginning of treatment. The frequent return strategy was elaborated to be introduced during the early stages of treatment, and showed the potential to achieve positive results.

Since the present study was based on secondary data, we were unable to investigate the reason for dropout reported by the patients. Prior studies attempting to identify factors associated to dropout report that the frequent return strategy could improve patient adherence to treatment. For example, Menzies et al,[6] in Canada, showed that longer intervals between the beginning of treatment and the first return were associated with greater risk of dropout, and that greater understanding of disease and treatment by the patient was associated with greater adherence. In Mexico, a qualitative study by Alvarez-Gordillo et al[1] emphasized the role of healthcare services in the relationship with patients and their relatives as an important factor for treatment dropout. In this study, dropout was also related to the adverse effects of treatment.[1]

In Rio de Janeiro, Natal et al[8] associated greater dropout, which occurs especially during the first half of the treatment period, with clinical improvement, and with lack of understanding of the disease and of the importance of treatment. This would be due to the poor relationship between physician and patient. These authors suggest that the "standardization of tuberculosis treatment led erroneously to the standardization of patient care and to the brutalization of relationships." In their conclusions, the authors suggest that a measure potentially capable of reducing dropout rates would be to reduce intervals between medical appointments for patients at greater risk.

The frequent return strategy provided an opportunity to improve the relationship between patient, physician, and healthcare facility, at a moment in which this link begins to be consolidated, and this seems to play an important role in patient adherence to treatment. The patient's appointments and visits to the healthcare facility are appropriate occasions for answering doubts concerning the disease and its transmission, treatment and its duration, and any others the patient may have. Side effects that were often considered as 'banal,' but which could even so lead to dropout were also identified. Other patients may have felt 'cured' as soon as symptoms receded, and, for these patients, it may have been necessary to further explain the importance of continuing treatment.

In the case of the Ubatuba program, one can infer that frequent returns worked initially as a preventive strategy for improving adherence to tuberculosis treatment. Subsequently, this strategy worked as a screening instrument, identifying patients in need for supervised treatment. A few patients, in spite of the opportunity to establish a good relationship with their physicians, showed signs of poor adherence to treatment. Patients who missed their weekly appointments already during the early stages of treatment and/or who were perceived to administer their medication irregularly were referred to supervised treatment.

Menzies et al[6] found that an initial interview conducted by a nurse from the tuberculosis program and the notes taken during this interview were important for the identification of patients at greater risk of dropout. The authors warn as to limitations in the generalization of their findings, since no standardized protocols for evaluating adherence were employed, but suggest that it was possible to

identify patients at risk of dropout already in the early stages of treatment.

This opportunity to identify potential cases of non-adherence, also at risk of abandoning treatment completely, optimized the investment of human, material, and financial resources on supervised treatment. Deheinzelin et al[3] also suggested that if DOTS were employed only to the population at risk of dropout, there could be a significant reduction in cost without loss in the efficacy of the strategy.

According to the literature,[12] healthcare services are unable to safely predict which cases will dropout from treatment. This was one of the reasons that led WHO to recommend that DOTS be used in all tuberculosis cases. It is possible that the large majority of services that treat patients with tuberculosis did not adopt strategies to improve the relationship with the patient. In Ubatuba, the frequent returns strategy may provide the physician with an opportunity to identify patients at risk of dropout.

Other health service-related factors influenced adherence to treatment. The quality and organization of the facility are pointed out by a number of authors as directly related to dropout. Deheinzelin et al[3] report that a tightening of the physician-patient relationship, the organization of patient care – leading to the reduction of waiting time before appointments –, and the specific training of physicians in tuberculosis care are important factors in maintaining good adherence. Natal et al[8] and Lima et al[5] found excessive waiting periods to be a frequent complaint amongst dropouts. Extended waiting periods within the facility discourage patients from returning to the service, and maybe even from adhering to treatment, especially among patients who become asymptomatic soon after the beginning of treatment. Excessive waiting would also hinder the use of the frequent return strategy, for the patient would also have to wait for appointments more often, thus favoring dropout from treatment.

The organization and investment in quality seen among health services in Ubatuba after 1997 have contributed to the improvement of tuberculosis diagnosis and consequently of the care provided to patients. Patients with positive sputum bacterioscopy tests may have felt greater confidence regarding their diagnosis, possibly leading to greater adherence to treatment. In agreement with this hypothesis is a study[8] conducted in Rio de Janeiro, which found greater risk of dropout among patients with negative bacterioscopies.

Tuberculosis is closely related to poverty, social issues, and access to healthcare.[8,15] The present study corroborates this idea, showing associations with illiteracy and unemployment, which increase the risk of dropout by approximately three times. When analyzed simultaneously, these factors showed an important reduction in the odds ratios for dropout, probably due to the relationship of these variables with each other and with the socioeconomic level of the population.

In the present study, patients considered as addicted to alcohol (alcoholics according to the notification forms) were almost four times more likely to abandon treatment. Alcohol dependence was the strongest predictor of dropout from treatment, and the only one to show only a small reduction after multivariate analysis. This association is already well known and has been widely reported in the literature.[3-5,9]

The clinical severity of the case may be associated with treatment dropout, thus working as a confounder for other variables, such as, for instance, hospital admissions and extra-pulmonary presentations. There was a trend towards protection from dropout among cases with extra-pulmonary clinical presentations and among cases admitted to the hospital at least once. Menzies et al[6] reported that short hospitalization periods (mean=17 days) at the beginning of treatment may provide an important benefit in increasing adherence to treatment. However, these authors point out that these results may have been confounded during analysis with the severity of the clinical presentation due to small numbers. Other studies[8] have shown increased risk of dropout after hospital discharge, since the latter may be understood by the patient as discharge from treatment.

The frequent return strategy played a fundamental role in the reduction of dropout rates and, consequently, in the increase of cure rates. The importance of the present study is in showing that there are alternatives to supervised treatment for all patients – the strategy recommended by WHO and by the Ministry of Health. We saw, at least in the municipality of Ubatuba, the development of a strategy that may be effective in the reduction of dropout rates.

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