Original Article

Analysis of treatment outcomes related to the tuberculosis control program in the city of Campinas, in the state of São Paulo, Brazil*

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Background: Tuberculosis cure is dependent upon treatment adherence.

Objective: To analyze the results of tuberculosis treatment in public health clinics in the city of Campinas, in the state of São Paulo, Brazil, during 2002.

Method: From a cohort of 484 patients diagnosed with tuberculosis, we evaluated 436. Treatment outcomes were described for all patients, whether new patients or patients in retreatment, including those presenting the pulmonary form, with or without acquired immunodeficiency syndrome (AIDS) comorbidity.

Results: The success rate was 68.6% (72.3% among non-AIDS patients and 57.6% among AIDS patients). Among new cases, the non-AIDS group presented a 2.2-times greater chance of presenting favorable results. In the AIDS group, no differences were observed between new patients and those in retreatment. Among the unfavorable outcomes, only lethality presented a difference (18.9% among AIDS patients and 8.0% among non-AIDS patients). In patients presenting the pulmonary form, the success rate was similar between those who were initially acid-fast bacilli positive and those who were not.

Conclusion: The tuberculosis control program in Campinas presented low effectiveness. In comparison to the 2001 national cohort, success rates were higher for non-AIDS patients but lower for AIDS patients. The higher success rate among cases of tuberculosis without AIDS was primarily derived from the treatment of new cases. The unfavorable profile of tuberculosis patients co-infected with AIDS, characterized by the (18.9%) lethality and the (15.3%) noncompliance, were partially responsible for the lower success rate seen among such patients. It is notable that such high proportions of noncompliant patients were seen in a city providing easy access to treatment. In order to improve the program, medical teams should receive further training in supervised treatment, health education and techniques for interacting with patients, all of which will require considerable investment.

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INTRODUCTION

Although tuberculosis (TB) is a severe disease, it is curable in virtually 100% of new cases if chemotherapy principles are followed[1]. Due to the existence of different bacterial populations, in distinct metabolic situations and reacting diversely to medication[2], that easily become resistant when chemotherapy is inappropriate[3], it is necessary to combine at least three drugs at the beginning of the treatment.

In Brazil, the *Programa de Controle da Tuberculose* (PCT, Tuberculosis Control Program)[4] recommends breaking the chain of disease transmission as one of the eradication strategies. The effectiveness of the PCT depends on both the percentage of patients who complete the treatment and the efficacy of the medication[5].

Currently, the biggest problem encountered in TB treatment is patient noncompliance[6]. As a result, the indicators of incidence, mortality and multidrug resistance are rising[7], and this is currently the principal cause for concern among health care professionals worldwide. A patient who abandons TB treatment becomes a major source of transmission of the bacillus, especially to individuals infected with human immunodeficiency virus (HIV).

In this context, an increasing understanding of certain quantitative data regarding treatment results has become relevant due to the consequences these data have for individual and collective action. The need to monitoring the PCT through periodic evaluation of treatment outcomes, together with the growing need for research into TB in the city of Campinas (SP), motivated the present study, which aims to analyze the results of TB treatment in public health clinics in the city of Campinas during 2002.

METHODS

Treatment outcomes of the cohort of individuals enrolled in the PCT in 2002 in the city of Campinas were analyzed using data from the Epidemiological Surveillance Database of the *Universidade Estadual de Campinas* (UNICAMP, Campinas State University). The information in this database came from the *Sistema Nacional de Agravos de Notificação* (SINAN, National Case Registry) through the Campinas Municipal Department of Health.

The patients in the 2002 cohort began treatment between 1 January and 31 December 2002.

In the variable "admission status"[4], patients were classified as "new cases" (in which no specific treatment had previously been administered) or "retreatment cases", (those who reentered the PCT due to relapse, prior noncompliance or previous treatment failure).

Not all TB patients undergo HIV testing, which appears on the SINAN form as "HIV testing not performed". Data on the number of patients with acquired immunodeficiency syndrome (AIDS) were obtained from the fields "associated diseases" and "HIV test results".

Treatment completion was determined as follows: in the seventh month for patients presenting pulmonary forms, extrapulmonary forms and AIDS comorbidity; in the tenth month for special situations such as TB and diabetes, chronic use of corticosteroids, post-gastrectomy, chronic kidney disease, etc.; and in the thirteenth month for patients under treatment regimens for treatment failure or for meningitides.

Treatment outcomes were classified[4] as "cure/treatment complete", "noncompliance", "transfer", "mortality" or "treatment failure". "Cure/treatment complete" was defined as two negative sputum smears, one in the follow-up phase and one in the final assessment. This group also included those patients who presented sputum smears negative for acid-fast bacilli (AFB) at the beginning of the treatment and took the medication for the prescribed length of time (treatment complete/cure not confirmed). The term "noncompliance" was used to describe cases in which the patient failed to appear in the clinic for more than 30 consecutive days after the scheduled appointment. When the patient was transferred to another health clinic, the outcome was defined as "transfer". Outcomes were classified as "mortality" if a patient death was reported during the treatment, regardless of the cause. "Treatment failure" was defined as positive sputum smears throughout the treatment period or until the fourth month.

The favorable outcomes, represented by the cures and treatments completed, were compared to the unfavorable outcomes (noncompliance, mortality, transfer and treatment failure). The dichotomous favorable/unfavorable-outcome variable was determined based on exposure factors: admission status (new case/retreatment), AIDS comorbidity and (in patients presenting the pulmonary form) sputum smear microscopy results.

Of the 484 patients enrolled in the PCT, 37 were excluded because their treatment outcomes were not registered in the SINAN, 6 were excluded because they were diagnosed as being infected

with atypical mycobacteria, and 5 were excluded because they were still under treatment. Therefore, the final study sample consisted of 436 patients.

The database containing data related to the patients who entered treatment in 2002 was analyzed using proportions, comparison of proportions, odds ratio (OR) with a 95% confidence interval (95% CI) and the chi-square test with Yates' correction. The software Epi Info 6.04 d was used for this analysis. The level of significance adopted was d" 5%.

RESULTS

Of the 436 TB patients, 111 (25.5%) presented concomitant AIDS (Table 1). New patients numbered 360 (82.6%), compared to 76 (17.4%) who were patients in retreatment (Table 2). AIDS concomitance was seen in 23.6% (85/360) of the new patients and 34.2% (26/76) of the patients in retreatment (Table 2). A total of 364 (83.5%) of the patients presented the pulmonary form and 73 (16.8%) presented the extrapulmonary form (Table 3).

The success rate (cure/treatments complete) was 68.6% (299/436): 72.3% (235/325) among non-AIDS patients and 57.6% (64/111) among AIDS patients. This finding shows that the PCT was more effective for non-AIDS patients (OR = 1.92; 95% CI = 1.20 - 3.08; $p = 0.0059$) (Table 1).

Among new patients and patients in retreatment, the effectiveness profile of treatment provided by the PCT differed between AIDS patients and non-AIDS patients. The success rate was higher in the group of new patients without AIDS than in the group of new patients with AIDS (74.9% vs. 54.1% or 206/275 vs. 46/85; $\div^2 = 13.37$; p = 0.0002). The non-AIDS group presented a 2.2-times greater chance of presenting favorable results among new cases (OR = 2.2; 95% CI = 1.11 - 4.22; p = 0.0222). In the AIDS group, no differences were observed between new patients and those in retreatment regarding treatment success (OR = 0.52; 95% CI = 0.18 - 1.46; p = 0.2551) (Table 2).

Table 4 shows the analysis of the unfavorable outcomes (noncompliance, mortality, treatment failure and transfer) in the AIDS and non-AIDS groups. Comparison of these outcomes revealed that only mortality presented a significant difference: 18.9% (21/111) among AIDS patients and 8.0% (26/325) among non-AIDS patients ($\div 2 = 10.26$; p = 0.0014). Noncompliance, transfer and treatment failure presented no significant differences.

In Table 4, we can also see that, when patients were stratified into new cases and retreatment cases, noncompliance was 8.9% (32/360) among new patients and 22.4% (17/76) among patients in retreatment. Patients in retreatment presented a 3-times greater chance of being noncompliant (OR = 3; 95% CI = 1.46 - 5.92; p = 0.0015).

TABLE 1

Effectiveness of the treatment provided through the Tuberculosis Control Program for tuberculosis patients with and without AIDS

Comorbidity	Success	Failure	Total
With AIDS	235	90	325
Without AIDS	64	47	111
Total	299	137	436

OR = 1.9; 95% CI: 1.20 - 3.08; p = 0.0059

TABLE 2

Effectiveness of the treatment provided through the Tuberculosis Control Program for tuberculosis patients with and without AIDS by admission status

Admission status	With AIDS (n = 111)			Without AIDS (n = 325)			
	Tt success	Tt failure	Subtotal	Tt success	Tt failure	Subtotal	Total
New cases	46	39	85	206	69	275	360
Retreatment cases	18	8	26	29	21	50	76
Total	64	47	111	235	90	325	436

OR (with AIDS) = 0.52; 95% CI: 0.18 - 1.46; p = 0.2551
OR (without AIDS) = 2.2; 95% CI: 1.11 - 4.22; p = 0.0222
Tt: treatment.

TABLE 3

Effectiveness of the treatment provided through the Tuberculosis Control Program for pulmonary tuberculosis patients, according to sputum smear microscopy

Pulmonary tuberculosis	Success	Failure	Total
Sputum smear positive	153	67	220
Sputum smear negative or not performe	101	43	144
Total	254	110	364

OR = 0.97; 95% CI: 0.60 - 1.58; p = 0.9969

The analysis of treatment outcomes, co-infection with AIDS and admission status (Table 4) revealed that, among new cases, noncompliance was 15.3% (13/85) in the AIDS group and 6.9% (19/275) in the non-AIDS group ($\div^2$ = 5.64; p = 0.0176). In the same group (new cases), mortality was 22.4% (19/85) in the AIDS group and 8% (22/275) in the non-AIDS group - a significant difference ($\div^2$ = 13.25; p = 0.0003). Among patients in retreatment, no differences regarding treatment outcomes were observed between AIDS and non-AIDS patients.

Table 3 shows the effectiveness of the PCT in the treatment of patients presenting the pulmonary forms. There was no difference in the success rate between those who were initially AFB positive and those who were not (OR = 0.97; 95% CI = 0.60 - 1.58; p = 0.9969). Similarly, when AIDS and non-AIDS patients were compared, no significant difference was found.

Table 5 shows the stratification of the treatment outcomes in patients with the pulmonary forms based on sputum smear microscopy results. Mortality was significantly higher among patients who were AFB negative and among those who did not undergo the exam (22/144) than among those who were AFB positive (15/220) (15.3% vs. 6.8%; $\div^2$ = 6.82; p = 0.0090). The other outcome groups did not present any significant differences regarding the sputum smear microscopy results.

DISCUSSION

The development of efficacious chemotherapy for TB was one of the greatest medical advances of the twentieth century. Rouillon et al.[1] state that the use of antibacterial drugs completely changes the natural evolution of TB. It not only increases survival rates and makes cure possible but also considerably reduces the period of infectiousness, prevents recurrence and eliminates chronic cases. However, this efficaciousness is partially reduced since patients do not always complete the treatment successfully. Campaigns to control TB aim to detect 70% of the expected cases and cure at least 85% of the diagnosed cases[4,5].

The World Health Organization, in its eighth report (2004) [7], in which the 2001 cohort is analyzed, reports that the treatment success rate was low in three countries (< 70%): Russia, Uganda and Brazil (67%). The situation was similar in the city of Campinas: in 2002 the PCT presented low effectiveness, with a success rate of only 68.6%. Campinas is a city where there is easy access to treatment and there are public health services, including two medical schools, providing decentralized TB treatment. This leads us to expect that the result would be different from what was determined. Although the Directly Observed Treatment, Short-course strategy has proved to be effective in several parts of the world[8,9], it is still in the implementation phase in the city.

TABLE 4

Distribution of tuberculosis patients by AIDS comorbidity and treatment outcome

Treatment outcome	With AIDS			Without AIDS			
	New	Retreat/	Subtotal	New	Retreat/	Subtotal	TOTAL
Cure/treatment complete	46	18	64	206	29	235	299
Noncompliance	13	4	17	19	13	32	49
Mortality	19	2	21	22	4	26	47
Transfer	7	1	8	27	4	31	39
Treatment failure	0	1	1	1	0	1	2
Total	85	26	111	275	50	325	436

TABLE 5

Distribution of pulmonary tuberculosis patients by sputum smear microscopy results and treatment outcome

Treatment outcome	Sputum smear positive	Sputum smear negative or not performed	Total
Cure/treatment complete	153	101	254
Noncompliance	30	13	43
Mortality	15	22	37
Transfer	20	8	28
Treatment failure	2	0	2
Total	220	144	364

In Campinas, success rates were different for AIDS patients than for non-AIDS patients, showing the importance of stratifying the cohort according to this variable in the analysis of effectiveness. Much higher treatment success rates were seen in non-AIDS patients than in AIDS patients (72.3% and 57.6%, respectively). In comparison to the 2001 national cohort[7], the effectiveness of the treatment provided through the PCT was higher for non-AIDS patients than for AIDS patients.

The success rate among non-AIDS TB cases was primarily derived from the positive outcomes of the treatment of new cases, in which the chance of presenting favorable results was 2.2-times greater than in the retreatment group.

In the 2001 Brazilian cohort[7], the success rate among patients in retreatment was 47%. Campos et al.[10] observed the same proportion of favorable results in the city of Recife (PE) in 1997. In the present study, 47 (61.8%) of the 76 patients in retreatment were cured or completed the treatment. This rate was higher than the national rate, as well as that recorded for Campinas in the 1993-1994 period, when the rate was lower than 50%[11]. In the comparison between TB patients with AIDS comorbidity in retreatment between 1993 and 1994 and those evaluated in the present study, mortality was seven times higher in the 1993-1994 period, indicating that the increased rates of success may be related to decreased mortality among AIDS patients as a result of the use of antiretroviral drugs.

In the present study, the success rate among patients who presented the pulmonary forms and were AFB positive was 69.5%. This rate was higher than the 54% seen in the 2001 Brazilian cohort[7] but much lower than the 80.9% obtained by Diel & Niemann in Hamburg, Germany[12] between 1997 and 2001 and the 77.2% obtained by El-Sony et al.[13] in Sudan. The higher mortality observed among patients presenting unconfirmed pulmonary forms merits more in-depth study since these patients would be expected to have better prognoses. It is possible that, in the routine practices of health services, other diseases have been incorrectly treated as TB.

In the categorization of unsuccessful cases, the unfavorable profile of TB patients with AIDS comorbidity, characterized by high mortality (18.9%) and noncompliance (15.3%), was partially responsible for the lower success rate seen among such patients. A study carried out in Sudan[13] did not include critical patients but showed higher mortality among new TB patients with comorbid AIDS (12% among HIV-positive individuals and 1.8% among HIV-negative individuals).

A limitation to the present study was the number of patients who were excluded due to the lack of information regarding treatment outcomes. The recording of information is not satisfactory, and this may even worsen the statistics since noncompliant cases would undoubtedly be included among these patients about whom there was no information. Another limitation was the partial lack of HIV serology data, which may lead to an underestimation of the rate of TB-AIDS comorbidity. In view of the importance of comorbidity data in devising appropriate treatment strategies, attempts should be made to perform HIV testing in 100% of the cases. The transfer situation also deserves special care since the final outcome for these patients (cure, death or noncompliance) is unknown.

The high rates of noncompliance, especially among patients in retreatment, demand that health clinics retool in order to achieve higher treatment adherence[6], taking into consideration the fact that compliance depends on several factors[6,14,15]. According to Gonçalves et al., some individuals may be led to believe that the disease is cured and abandon the treatment when the symptoms disappear. In addition, through association mechanisms, some patients believe that taking the medication would revive the disease and the limitations imposed by it on their daily routine - limitations that they would like to forget.

Interaction between physicians and patients has also been identified as important. Patients who do not trust the health system or the physician are more likely not to adhere to the medication regimen[16]. It is important to bear in mind that noncompliance is directly related not only to the dissemination of the disease but also to the development of multidrug-resistant strains[6]. The appropriate combination and supervised use of correct doses for a sufficient length of time is the best means of preventing bacterial persistence and the development of drug resistance, thereby ensuring the cure of the patient.

Health education[17] is one of the strategies used to reduce the rate of noncompliance and, consequently, the indicators cited. The importance of organized and accessible health services in the care of TB patients cannot be overemphasized. During consultation and education activities, personal patient issues must be taken into account, bearing in mind that each individual is unique and has his/her own history, values and beliefs.

Improving the effectiveness of the PCT in Campinas and achieving the goal set by the World Health Organization will require modifying not only physician-patient interaction but also the interaction of all members of the medical team with the patient. In addition, health education programs aimed at the patients and their families should be implemented or refined. The teams should perform sputum smear microscopy whenever there is cough and expectoration. Finally, in view of the lower success rate among TB patients with AIDS comorbidity and in addition to the considerations above, special care should be taken to monitor interaction between the medical team and these patients as well as to supervise treatment.

REFERENCES

1. Rouillon A, Perdrizet S, Parrot R, Waaler H. Métodos de control de la tuberculosis. La transmisión del bacilo tuberculoso. El efecto de la quimioterapia. WHO/Tb,1977;346:1-30.
2. Grosset J. Bacteriological basis of chemotherapy of tuberculosis. In: III Regional Seminar on Tuberculosis Chemotherapy. Paho,1979;1-10.
3. Mitchison DA. The action of antituberculosis drugs in short-course chemotherapy. Tubercle 1985;66:219-25.
4. Ministério da Saúde. Fundação Nacional de Saúde. Controle da tuberculose: uma proposta de integração ensino-serviço. FUNASA/CRPHF/SBPT,2002; 1-236.
5. World Health Organization. Treatment of tuberculosis: Guidelines for national programmes. WHO/CDS/TB, 1997;1-78.
6. World Health Organization. Adherence to long-term therapies:evidence for action. Tuberculosis. WHO, 2003;123-30
7. World Health Organization. WHO Report 2004. Global Tuberculosis Control [cited 2004 may 02]. Available from: www.who.int/tb/publications/global_report/2004/en/.
8. Khatri GR, Frieden TR. Controlling tuberculosis in India. N Engl J Med 2002;347:1420-5.
9. Ruohonen RP, Goloubeva TM, Trnka L, Fomin MM, Zhemkova GA, Sinitsyn AV, Lichachev AA, Koskela KG. Implementation of the DOTS strategy for tuberculosis in the Leningrad Region, Russian Federation (1998-1999). Int J Tuberc Lung Dis 2002;6:192-7.
10. Campos HMA, Albuquerque MFM, Campelo ARL, Souza W, Brito AM. O retratamento da tuberculose no município do Recife, 1997: uma abordagem epidemiológica. J Pneumol 2000;26:235-40.
11. Oliveira HB, Moreira Filho DC. Abandono de tratamento e recidiva da tuberculose: aspectos de episódios prévios, Campinas,SP, Brasil, 1993-1994. Rev Saúde Pública 2000;34:437-43.
12. Diel R, Niemann S. Outcome of tuberculosis treatment in Hamburg: a survey, 1997-2001. Int J Tuberc Lung Dis 2003;7:124-31.
13. El Sony AL, Khamis AH, Enarson DA, Baraka O, Mustafa SA, Bjuna G. Treatment results of DOTS in 1797 sudanese tuberculosis patients with or without HIV co-infection. Int J Tuberc Lung Dis 2002;6:1058-66.
14. Costa JSD, Gonçalves H, Menezes AMB, Devens E, Piva M, Gomes M, Vaz M. Controle epidemiológico da tuberculose na cidade de Pelotas, Rio Grande do Sul, Brasil: adesão ao tratamento. Cad. Saúde Pública 1998;14:409-15.
15. Sumartojo E. When tuberculosis treatment fails. A social behavioral account of patient adherence. Am J Respir Dis, 1992;68:49-59.
16. Gonçalves H, Costa JSD, Menezes AMB, Knauth D, Leal OF. Adesão à terapêutica da tuberculose em Pelotas, Rio Grande do Sul: na perspectiva do paciente. Cad. Saúde Pública 1999;15:777-87.
17. Levy SN, Silva JJC, Cardoso IFR, Werberich PM, Moreira LLS, Montiani H, Carneiro RM. Educação em Saúde: Histórico, conceitos e propostos. Conferência Nacional de Saúde. Ministério da Saúde. Diretoria de Programas de Educação em Saúde. [cited 2004 May 02]. Available from: http://www.datasus.gov.br/cns/datasus.htm.