Outcome of pulmonary tuberculosis treatment in the tertiary care setting — Toronto 1992/93

Evidence

Études

Wendy Wobeser, MD, MSc; Lilian Yuan, MD, MSc; Monika Naus, MD, MSc; and the Tuberculosis Treatment Completion Study Group*

Abstract

Background: Completion of treatment of active cases of tuberculosis (TB) is the most important priority of TB control programs. This study was carried out to assess treatment completion for active cases of pulmonary TB in Toronto.

Methods: Consecutive cases of culture-proven pulmonary TB were obtained from the microbiology laboratories of 5 university-affiliated tertiary care centres in Toronto in 1992/93. A standard data-collection tool was used to abstract information from inpatient and outpatient charts. For patients who were transferred to other treatment centres or lost to follow-up, the local health unit was contacted for information about treatment completion. If incomplete information was obtained from these sources, data from the provincial Reportable Disease Information System were also reviewed. The main outcome analysed was treatment outcome, with cases classified as completed (record of treatment completion noted), transferred (patient transferred to another centre but no treatment results available), defaulted (record of defaulting in patient chart but no record of treatment completion elsewhere, or patient still receiving treatment more than 15 months after diagnosis) or dead (patient died before treatment completion).

Results: Of the 145 patients 84 (58%) completed treatment, 25 (17%) died, 22 (15%) defaulted and 14 (10%) were transferred. The corresponding values for the 22 patients with HIV coinfection were 6 (27%), 5 (23%), 8 (36%) and 3 (14%). Independent predictors of failure to complete treatment were injection drug use (adjusted odds ratio [OR] 5.7, 95% confidence interval [CI] 1.5 to 22.0), HIV infection (adjusted OR 4.6, 95% CI 1.4 to 14.7) and adverse drug reaction (adjusted OR 2.9, 95% CI 1.1 to 7.9). Independent predictors of death included age more than 50 years (adjusted OR 16.7, 95% CI 2.6 to 105.1), HIV infection (adjusted OR 16.1, 95% CI 3.9 to 66.4), immunosuppressive therapy (adjusted OR 8.0, 95% CI 1.9 to 34.4) and infection with a multidrug-resistant organism (adjusted OR 30.7, 95% CI 1.5 to 623.0).

Interpretation: Treatment completion rates in tertiary care hospitals in Toronto in 1992/93 were below the rate recommended by the World Health Organization. Careful surveillance of treatment completion is necessary for the management of TB in metropolitan centres in Canada.

Résumé

Contexte : L'achèvement du traitement dans les cas actifs de tuberculose constitue la priorité la plus importante des programmes de lutte contre la tuberculose. Cette étude visait à évaluer l'achèvement du traitement dans des cas actifs de tuberculose pulmonaire à Toronto.

Méthodes : On a obtenu des cas consécutifs de tuberculose pulmonaire, démontrée par une culture, des laboratoires de microbiologie de cinq centres de soins tertiaires affiliés à l'Université de Toronto en 1992/1993. On a utilisé un outil standard de collecte de données pour résumer l'information tirée des dossiers de patients hospitalisés et de patients en service externe. Dans le cas des patients transférés à d'autres centres de traitement ou perdus au cours du suivi, on a

Dr. Wobeser is with the Department of Medicine, Queen's University and Kingston General Hospital, Kingston, Ont.; Dr. Yuan is Assistant Professor with the Department of Public Health Sciences, University of Toronto, Toronto, Ont.; and Dr. Naus is Physician Manager, Disease Control Service, Public Health Branch, Ontario Ministry of Health, Toronto.

**Members: Drs. Charles K.N. Chan, Wellesley Hospital and The Toronto Hospital; Jeffrey D. Edelson, St. Michael's Hospital; Donald E. Low, Mount Sinai Hospital; Irving E. Salit, The Toronto Hospital; and Andrew E. Simor, Sunnybrook and Women's College Health Sciences Centre, Toronto, Ont.*

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communiqué avec l'unité sanitaire locale pour obtenir de l'information sur l'achèvement du traitement. Si l'information obtenue de ces sources était incomplète, on a aussi étudié des données tirées du système provincial d'information sur les maladies à déclaration obligatoire. Le principal résultat analysé a été le résultat du traitement et les cas ont été classés ainsi : terminés (achèvement du traitement dûment noté au dossier), transférés (patient transféré à un autre centre mais aucun résultat de traitement disponible), en situation de défaut (note sur la situation de défaut consignée au dossier du patient, mais aucune mention d'achèvement du traitement ailleurs, ou patient qui suit encore des traitements plus de 15 mois après le diagnostic) ou morts (patient mort avant la fin du traitement).

Résultats : Sur les 145 patients, 84 (58 %) ont terminé le traitement, 25 (17 %) sont morts, 22 (15 %) étaient en situation de défaut et 14 (10 %) ont été transférés. Les valeurs correspondantes dans le cas des 22 patients qui étaient aussi infectés par le VIH étaient : 6 (27 %), 5 (23 %), 8 (36 %) et 3 (14 %). Les prédicteurs indépendants de non-achèvement du traitement étaient la consommation de drogues injectées (rapport des cotes [RC] rajusté de 5,7, intervalle de confiance [IC] à 95 %, 1,5 à 22,0), l'infection par le VIH (RC rajusté de 4,6, IC à 95 %, 1,4 à 14,7) et les effets indésirables de médicaments (RC rajusté de 2,9, IC à 95 %, 1,1 à 7,9). Les prédicteurs indépendants de décès comprenaient l'âge de plus de 50 ans (RC rajusté de 16,7, IC à 95 %, 2,6 à 105,1), l'infection par le VIH (RC rajusté de 16,1, IC à 95 % de 3,9 à 66,4), une thérapie immunosuppressive (RC rajusté de 8,0, IC à 95 %, 1,9 à 34,4) et une infection par un organisme résistant à de multiples médicaments (RC rajusté de 30,7, IC à 95%, 1,5 à 623,0).

Interprétation : Les taux d'achèvement du traitement dans les hôpitaux de soins tertiaires de Toronto en 1992/1993 étaient au-dessous du taux recommandé par l'Organisation mondiale de la santé. Il faut surveiller attentivement l'achèvement du traitement pour prendre en charge la tuberculose dans les centres métropolitains au Canada.

Completion of treatment of active cases of tuberculosis (TB) is the most important priority of TB control programs. Guidelines suggest a target of treatment completion of 85% for infectious cases of TB.[1] In 1994 the World Health Organization (WHO) estimated the rate of treatment success to vary from 77% in areas instituting WHO TB control strategies (which include the use of directly observed therapy) to 41% in areas without such strategies.[1]

The treatment completion rate in Montreal in 1987/88 was reported as 92% for culture-positive TB.[2] A total of 67% of patients with smear-positive pulmonary TB diagnosed in 1992 in British Columbia completed treatment.[3] Treatment completion rates have not been published for Ontario. The incidence rate of TB in Toronto is among the highest in the country (23 per 100 000 in 1995).[4] The treatment of TB in Ontario is done in a decentralized, integrated fashion. Treatment completion is monitored primarily by the treating physician and followed by the public health unit. For regimens that are not observed directly, treatment completion can be estimated only indirectly.

Noncompletion of treatment has serious consequences, including ongoing infectiousness and development of drug-resistant *Mycobacterium tuberculosis*. No reliable way exists to predict which patient will complete and adhere to TB treatment. Nonadherence does not correlate well with patient characteristics such as education level, socioeconomic status, age, sex and marital status.[5] However, failure to complete treatment has been associated with alcohol abuse, drug abuse and homelessness.[6,7] Patients with AIDS have been found to be more likely than those without AIDS to complete treatment.[6]

To estimate treatment completion rates and to identify predictors of failure to complete therapy in Toronto, we evaluated cases of culture-confirmed pulmonary TB at 5 tertiary care hospitals.

Methods

Consecutive cases of microbiologically confirmed pulmonary TB diagnosed in 1992/93 were obtained from the microbiology laboratories of 5 university-affiliated tertiary care hospitals in Toronto. Patients with isolated pleural disease were excluded from analysis. Ethics approval for the study was obtained from the University of Toronto and the ethics review board of each hospital. We used a standard data-collection tool to collect information from both inpatient and outpatient

charts. When patients receiving treatment for TB were transferred to other treatment centres or were lost to follow-up, we contacted the local health unit for information about treatment completion. If incomplete information was obtained from these sources, we reviewed the data available from the provincial Reportable Disease Information System (RDIS). The RDIS is a computerized system implemented in 1990 to contain information on cases of reportable diseases, including TB. Data collection and analysis were conducted during 1994–1997.

The main variable analysed was treatment outcome. Treatment outcome definitions, adapted from an international standard of classification,[8] were as follows: 1) completed (there was a record of having completed treatment in the inpatient, outpatient or health unit chart or the RDIS), 2) transferred (the patient was formally transferred to another treatment centre, and no treatment results were available from the health unit chart or the RDIS), 3) defaulted (there was a record of defaulting in the inpatient or outpatient chart, with no record of treatment completion in the health unit chart or the RDIS, or the patient was still receiving treatment more than 15 months after the diagnosis) and 4) dead (the patient died before completing treatment). For patients who died while still receiving treatment more than 15 months after the diagnosis, the final classification for the outcome analysis was "defaulted." Sputum microscopy results were not used for classification because follow-up sputum results were unavailable in most cases.

We used the χ^2 test to evaluate differences in categorical variables. Fisher's exact test was used when cell sizes were less than 5. We used Student's *t*-test to compare continuous variables and performed logistic regression analysis to identify predictors of noncompletion of treatment and death. Patients were categorized into those who completed and those who did not complete treatment. Noncompleters were those for whom treatment completion was not documented and included both those who clearly defaulted and those for whom treatment completion could not be documented as a result of transfer of care. When we repeated the analysis excluding the transferred patients from the noncompleter group, the results were similar. Patients who died while receiving treatment were excluded from the analysis. An adverse drug reaction was defined as any such reaction that resulted in a change of the TB treatment regimen. We constructed the multivariate model using factors that were found to be significant (*p* value of less than 0.05) on univariate analysis. Data analysis was carried out with Epi-Info 6 (US Centers for Disease Control and Prevention, Atlanta) and SPSS version 7.5 (SPSS Inc., Chicago).

Results

A total of 150 patients with pulmonary TB were enrolled. No treatment records could be found for 4 patients, and 1 patient was transferred before therapy was started. The remaining 145 cases were included in the analysis.

The patients were predominantly male (Table 1). Risk factors for TB were identified for 135 patients (93%); 51 (35%) had more than one risk factor. The predominant risk factor was birth outside Canada (102 patients [70%]), with the next most frequent being HIV infection, previous TB, homelessness and injection drug use. Other risk factors included diabetes mellitus, hematologic malignant disorder, renal failure, malnutrition, pneumoconiosis, immunosuppressive therapy and gastrectomy. Previous isoniazid preventive therapy was reported in 5 cases (3%).

The patients born outside Canada were less likely to have documented HIV infection, use injection drugs or be homeless than the patients born in Canada (Table 1). Among the former group the mean duration of residence in Canada was 10.8 (median 6.5) years.

The patients known to be HIV positive were younger and were more likely to be male than those not known to be HIV positive. For most of the HIV-positive patients their HIV status was known at the time TB was diagnosed. Only 26 (21%) of the 123 patients not known to be HIV positive at the time TB was diagnosed were screened for this coinfection; of the 26, 2 (8%) had a positive result.

Table 1: Characteristics of patients with pulmonary tuberculosis (TB) from 5 tertiary care centres in Toronto in 1992/93

Characteristic	Group: All patients *n = 145*	Group: Born outside Canada *n = 102*	Group: HIV positive *n = 22*
Mean (and median) age, yr*	45 (41)	45 (37)	35 (32)
No. (and %) male*	109 (75)	71 (70)	22 (100)
No. (and %) homeless†	14 (10)	5 (5)	1 (4)
No. (and %) injection drug user†	13 (9)	3 (3)	4 (18)
No. (and %) with previous TB	19 (13)	16 (16)	2 (9)
No. (and %) with > 1 risk factor	51 (35)	36 (35)	15 (68)
No. (and %) presented with symptoms	112/135 (83)	83 (81)	17 (77)
Mean (and median) duration of symptoms, wk*	12 (6)	13 (6)	6 (3)
No. (and %) with chest x-ray changes typical for TB*	82/125 (66)	64/95 (67)	4/20 (20)
No. (and %) with *Mycobacterium tuberculosis* resistant to ≥ 1 first-line agent	12/120 (10)	11/89 (12)	3/21 (14)
No. (and %) in hospital at time of diagnosis	91 (63)	60 (59)	16 (73)
Mean (and median) treatment duration for those who completed treatment, wk*	44 (40)	41 (40)	63 (53)

*$p < 0.05$, comparing HIV-infected patients and those without HIV infection.
†$p < 0.05$, comparing foreign-born and Canadian-born patients.

Overall, 83% (112/135) of the patients presented with symptoms (Table 1). The mean symptom duration at the time of diagnosis was 12 weeks. Symptom duration was shorter among those with HIV infection than among those without HIV infection ($p < 0.01$). Of the patients not known to be HIV positive and for whom chest x-ray results were available, 74% (84/114) presented with chest x-ray film changes typical for TB (upper lobe infiltrate or fibronodular disease). In contrast, only 20% (4/20) of the HIV-positive patients had typical changes on chest x-ray film ($p < 0.001$). In 4 cases (3%) the organism was resistant to both isoniazid and rifampin. One additional patient, who was HIV positive, manifested multidrug resistance while receiving therapy. Sputum examination was smear positive for 88 patients (61%); there was no difference in the results between the HIV-negative and HIV-positive groups. The mean treatment duration was longer for the HIV-positive patients than for those not known to be HIV infected (63 v. 40 weeks) ($p < 0.01$).

A total of 91 patients (63%) were in hospital at the time of diagnosis and treatment initiation. Thirteen different drug regimens were used. A standard regimen[9] was used for the initial therapy in 106 (75%) of 141 cases. The initial regimen contained rifampin for most patients (137 [97%]); pyrazinamide was used as part of the initial regimen for only 111 (79%). Of the 141 patients, 27 (19%) had an adverse drug reaction that resulted in a modification of the treatment regimen. Of the 27, 11 (41%) had hepatitis, 7 (26%) rash or pruritus, 5 (18%) gastrointestinal intolerance and, in 1 case (4%) each, arthralgia, fever, confusion and isolated hyperbilirubinemia.

For 127 (97%) of 131 patients for whom the physician who ordered the initial treatment regimen was identified, the physician was a specialist: in 66 cases the doctor was a respirologist, in 33 an infectious disease specialist and in 28 an internal medicine specialist. No relation was found between physician characteristics and either initial treatment regimen or outcome.

Of the 145 patients, 84 (58%) were known to have completed treatment, and 25 (17%) died before completing treatment (Table 2). Of the 22 HIV-positive patients, only 6 (27%) were known to have completed treatment, and 5 (23%) died before completing treatment. Of the 88 patients who were sputum smear positive, 48 (55%) completed treatment, 14 (16%) defaulted, 15 (17%) died, and 10 (11%) were transferred to another treatment centre.

Table 2: Treatment outcome by subgroup

	Group; no. (and %) of patients		
Outcome	All patients	Born outside Canada	HIV positive
Completed treatment	84 (58)	62 (61)	6 (27)
Transferred	14 (10)	10 (10)	3 (14)
Died	25 (17)	17 (17)	5 (23)
Defaulted*	22 (15)	13 (13)	8 (36)

*Record of defaulting in patient chart with no record of treatment completion elsewhere (e.g., health unit chart), or patient was still receiving treatment more than 15 months after diagnosis of TB.

Treatment failure

Factors that were found to predict failure to complete treatment on univariate analysis included injection drug use, HIV infection and adverse drug reaction. Factors that were not found to predict failure to complete treatment included birth outside Canada, homelessness, alcohol abuse, standard initial drug regimen, being in hospital at treatment initiation and multidrug resistance. Injection drug use (adjusted odds ratio [OR] 5.7, 95% confidence interval [CI] 1.5 to 22.0), HIV infection (adjusted OR 4.6, 95% CI 1.4 to 14.7) and adverse drug reaction (adjusted OR 2.9, 95% CI 1.1 to 7.9) were all found to be independent predictors of failure to complete treatment on multivariate analysis (Table 3).

Death

A total of 31 patients (21%) were known to have died. Three died before treatment was started, 25 died before completing treatment, 2 died while still receiving treatment more than 15 months after diagnosis (classified as "defaulted"), and 1 died after completing treatment (classified as "completed"). Of the 31 patients, 11 (35%) were known to be HIV positive, and 7 (23%) were receiving immunosuppressive therapy (after solid organ transplantation in 2 cases, as chemotherapy for adenocarcinoma [1 case] and hepatoma [1 case], and, in 1 case each, for idiopathic thrombocytopenic purpura, rheumatoid arthritis and asthma [prednisone in all 3 cases]). TB was felt to have contributed to death in 20 cases (65%). The mean time to death was longer for those infected with HIV than for those receiving immunosuppressive therapy (62 v. 35 weeks) ($p < 0.05$). Of the 31 patients, 4 were homeless and 3 were injection drug users. Independent predictors of death on multivariate analysis included age more than 50

Table 3: Predictors of failure to complete treatment on multivariate analysis*

Variable	Unadjusted odds ratio (and 95% CI)	Adjusted odds ratio (and 95% CI)
Injection drug use	5.5 (1.6–19.7)	5.7 (1.5–22.0)
HIV infection	5.5 (1.9–16.3)	4.6 (1.4–14.7)
Adverse drug reaction	3.3 (1.3–8.1)	2.9 (1.1–7.9)

Note: CI = confidence interval.
*Failure to complete = default (transferred or treatment completion not documented). Patients who died before completing treatment were excluded.

years (adjusted OR 16.7, 95% CI 2.6 to 105.1), HIV infection (adjusted OR 16.1, 95% CI 3.9 to 66.4), immunosuppressive therapy (adjusted OR 8.0, 95% CI 1.9 to 34.4) and multidrug resistance (adjusted OR 30.7, 95% CI 1.5 to 623.0) (Table 4).

Of the 4 patients with multidrug resistance initially, 3 died, with the mean time to death being 39 weeks. Two were HIV positive, both of whom died. In 2 of the 4 cases, the drug resistance was primary (no previous treatment), and in 2 cases it was secondary. The place of birth was known for 1 of the patients with primary resistance (China).

Interpretation

The rate of treatment completion in our study was well below recommended rates and also below the rate of 92% reported from Montreal.[2] Treatment completion rates may in reality have been better than what was estimated in this study, however. Treatment completion was unknown among the considerable number of patients who were transferred to other treatment centres. No records of treatment completion could be found despite extensive effort. It is imperative that such results be available centrally.

Our patients were enrolled from the 5 tertiary care centres in Toronto. Although the care they received may not represent TB management in the community, it may be expected to be superior given that these were university-affiliated centres. Overall, these 150 cases of culture-confirmed pulmonary TB represent 19% of all such cases in Ontario for 1992/93.

Although our patients were treated almost entirely by specialists in teaching hospitals, recommended treatment regimens[9] were adhered to only some of the time (in 25% of the cases the initial treatment was a regimen not considered standard by current guidelines). Possible reasons for use of such nonstandard regimens include concern about drug resistance, concern about potential drug interactions in HIV-infected and other immunocompromised patients who may be receiving other drugs, and lack of familiarity with current guidelines. We did not find that the initial treatment regimen was correlated with outcome. However, the use of nonstandard regimens may result in the development of drug resistance and increased risk of adverse drug effects.

The substantial proportion of patients who experienced adverse drug reactions necessitating a change in treatment regimen negatively affected treatment completion. This finding highlights the importance of appropriate prescription of drug combinations that are least likely to result in toxic effects. It also reinforces the need for continued research into simpler and safer chemotherapy regimens.

The high rate of treatment noncompletion among the HIV-infected patients in our study contrasts with reports of higher treatment completion rates among such patients in New York City.[6] Social infrastructure support, including incentives (e.g., financial support, child care support and transportation) and housing, is provided in some US cities for people with TB who are HIV positive. Infrastructure support plays an important role in ensuring treatment completion for marginalized groups, such as injection drug users and people infected with HIV.[10,11]

HIV infection markedly increases susceptibility to TB.[12] As well, HIV coinfection may influence treatment outcome. The frequency of HIV infection is higher among people with TB than in the general population.[13] In our study HIV infection was detected among 8% of those screened. However, only 21% of patients had a documented HIV test on record. Health care providers may not identify risk factors for HIV in many patients with TB.[14] It is therefore important to screen all patients with TB for HIV infection.[9]

Assessing adherence to treatment among the 15% of patients in our study who defaulted and the 10% who were transferred to other centres, for whom no information about treatment completion was available, was problematic. This situation suggests that gaps exist in the monitoring of treatment follow-up. High-quality data on treatment completion are essential to an effective TB control program.

Treatment completion is the cornerstone of successful TB control. Directly observed therapy is the best documented way to ensure adherence to prescribed regimens.[15–19] The WHO-recommended cure rate of 85% was attained in New York City after a program involving directly observed therapy was implemented.[10] This form of administering therapy may also result in reductions in drug resistance and relapse rates.[18] Consequently, it appears to be cost-effective.[16,17] TB programs may not have enough resources to ensure directly observed therapy for every case. In these instances, priority needs to be given to groups at greatest risk of transmitting disease and failing

Table 4: Predictors of death on multivariate analysis

Variable	Unadjusted odds ratio (and 95% CI)	Adjusted odds ratio (and 95% CI)
Age > 30 and ≤ 50 yr*	2.2 (0.7–7.8)	5.1 (0.9–29.1)
Age > 50 yr*	4.3 (1.2–13.1)	16.7 (2.6–105.1)
HIV infection	5.2 (2.0–14.0)	16.1 (3.9–66.4)
Immunosuppressive therapy	7.6 (2.3–26.2)	8.0 (1.9–34.4)
Multidrug-resistant *M. tuberculosis*	11.5 (1.1–117.8)	30.7 (1.5–623.0)

*Reference category = age ≤ 30 yr.

to complete treatment. In addition to patients with positive sputum smears, our results suggest that 3 other groups — injection drug users, HIV-infected patients and patients who experience adverse drug effects — should be considered high priority for directly observed therapy.

A program involving directly observed therapy was instituted in Toronto in 1995, and currently one-third of cases of active TB in this city are treated with this approach. It appears that rates of treatment completion in Toronto have improved since 1992/93 (Sharon Pollock, manager, communicable disease and epidemiology service, Public Health, City of Toronto: personal communication, 1998). However, other indicators of the TB control program at the provincial level suggest that problems may be persisting. Rates of resistance of *M. tuberculosis* isolates increased in Ontario between 1987 and 1996.[20] This may be attributable in part to other factors, such as immigration of people with drug-resistant organisms. However, nonadherence to therapy and poor completion rates are an important cause of drug-resistant *M. tuberculosis*.[21]

The costs of incomplete and inadequate treatment of TB are borne by the entire community. Resources need to be devoted to ensure adequate follow-up and completion of treatment. Careful ongoing surveillance will be required to optimize management of TB control programs and to prevent the emergence of multidrug-resistant TB as an important public health problem in Canada.

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References

1. Global Tuberculosis Programme. *Global tuberculosis control. WHO report 1997* [rep no WHO/TB/97.225]. Geneva: World Health Organization; 1997. p. 9-15.
2. Menzies R, Rocher I, Vissandjee B. Factors associated with compliance in treatment of tuberculosis. *Tuberc Lung Dis* 1993;74(1):32-7.
3. FitzGerald JM, Garcia-Cruz A, Elwood RK, Enarson DA. Cohort evaluation of treatment results, British Columbia [abstract]. *Tuberc Lung Dis* 1995;76 (Suppl 2):80.
4. Kerbel D. Epidemiology of tuberculosis in Ontario — 1995. *Public Health Epidemiol Rep Ont* [Ontario Ministry of Health] 1997;8(4):81.
5. Sumartojo E. When tuberculosis treatment fails. A social behavioral account of patient adherence. *Am Rev Respir Dis* 1993;147:1311-20.
6. Brudney K, Dobkin J. Resurgent tuberculosis in New York City. Human immunodeficiency virus, homelessness, and the decline of tuberculosis control programs. *Am Rev Respir Dis* 1991;144:745-9.
7. Slutkin G. Management of tuberculosis in urban homeless indigents. *Public Health Rep* 1986;101:481-5.
8. International Union Against Tuberculosis and Lung Disease. *Tuberculosis guide for low income countries*. 4th ed. Paris: IVATLD; 1996.
9. Standards Committee, Canadian Thoracic Society. *Canadian tuberculosis standards*. 4th ed. Thorold (ON): Canadian Lung Association; 1996.
10. Fujiwara PI, Larkin C, Frieden TR. Directly observed therapy in New York City. History, implementation, results, and challenges. *Clin Chest Med* 1997;18(1):135-48.
11. Schluger N, Ciotoli C, Cohen D, Johnson H, Rom WN. Comprehensive tuberculosis control for patients at high risk for noncompliance. *Am J Respir Crit Care Med* 1995;151:1486-90.
12. Hopewell PC. Impact of human immunodeficiency virus infection on the epidemiology, clinical features, management, and control of tuberculosis. *Clin Infect Dis* 1992;15:540-7.
13. Onorato IM, McCray E. Prevalence of human immunodeficiency virus infection among patients attending tuberculosis clinics in the United States. *J Infect Dis* 1992;165:87-92.
14. Barnes PF, Silva C, Otaya M. Testing for human immunodeficiency virus infection in patients with tuberculosis. *Am J Respir Crit Care Med* 1996;153: 1448-50.
15. Chaulk CP, Moore-Rice K, Rizzo R, Chaisson RE. Eleven years of community-based directly observed therapy for tuberculosis. *JAMA* 1995;274:945-51.
16. Burman WJ, Dalton CB, Cohn DL, Butler JR, Reves RR. A cost-effectiveness analysis of directly observed therapy vs self-administered therapy for treatment of tuberculosis. *Chest* 1997;112:63-70.
17. Moore RD, Chaulk CP, Griffiths R, Cavalcante S, Chaisson RE. Cost-effectiveness of directly observed versus self-administered therapy for tuberculosis. *Am J Respir Crit Care Med* 1996;154(4 pt 1):1013-9.
18. Weis SE, Slocum PC, Blais FX, King B, Nunn M, Matney GB, et al. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. *N Engl J Med* 1994;330:1179-84.
19. Iseman MD, Cohn DL, Sbarbaro JA. Directly observed treatment of tuberculosis. We can't afford not to try it [editorial]. *N Engl J Med* 1993;328:576-8.
20. Remis RS, Jamieson F, Haddad A, Chedore P, Vernich L. Increasing resistance of *M. tuberculosis* isolates, Ontario 1987–96 [abstract E-167]. In: *Program and abstracts — Interscience Conference on Antimicrobial Agents and Chemotherapy*. Washington: American Society for Microbiology; 1997.
21. Mahmoudi A, Iseman MD. Pitfalls in the care of patients with tuberculosis: common errors and their association with the acquisition of drug resistance. *JAMA* 1993;270:65-8.

Reprint requests to: *Dr. Wendy Wobeser, Department of Medicine, Queen's University, Connell 7, Kingston General Hospital, Kingston ON K7L 2V7; fax 613 548-6080*