Treatment Completion and Costs of a Randomized Trial of Rifampin for 4 Months versus Isoniazid for 9 Months

Dick Menzies, Marie-Josée Dion, Barry Rabinovitch, Sharyn Mannix, Paul Brassard, and Kevin Schwartzman

Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, and Division of Clinical Epidemiology, Royal Victoria Hospital, McGill University, Montreal, Quebec, Canada

There is little published information regarding treatment completion, safety, and efficacy of rifampin administered daily for 4 months—a recommended alternative to 9 months of isoniazid for therapy of latent tuberculosis infection. In an open-label randomized trial at a university-affiliated respiratory hospital, consenting patients whose treating physician had recommended therapy for latent tuberculosis infection were randomized to daily self-administered rifampin for 4 months or daily self-administered isoniazid for 9 months. Of 58 patients randomized to rifampin, 53 (91%) took 80% of doses, and 50 (86%) took more than 90% of doses within 20 weeks compared with 44 (76%) and 36 (62%) who took 80 and 90%, respectively, of doses of isoniazid within 43 weeks (relative risks: 80% of doses, 1.2 [95% confidence interval: 1.02, 1.4]; 90% of doses, 1.4 [1.1, 1.7]). Adverse events resulted in permanent discontinuation of therapy for two (3%) patients taking rifampin, and for eight (14%) patients taking isoniazid. Three patients developed drug-induced hepatitis—all were taking isoniazid. Total costs of therapy were significantly higher for isoniazid. In conclusion, completion of therapy was significantly better with 4 months of rifampin and major side effects were somewhat lower. Further studies are needed to assess the safety and efficacy of the 4-month rifampin regimen.

Keywords: latent tuberculosis infection; treatment of latent tuberculosis infection; tuberculosis prevention

A major activity of many tuberculosis (TB) control programs in industrialized countries is the identification of persons with latent TB infection (LTBI), who have increased risk of development of active TB. Treatment of such individuals can provide individual (1–6) and public health (4–8) benefits. The current recommended standard therapy is 9 months of isoniazid (9INH). This has an efficacy of more than 90% (9) if taken properly. However, because of the long duration, only 64–67% of patients (10, 11) or fewer (12) complete therapy under routine program conditions. Another limitation of INH is the occurrence of drug-induced hepatitis. Although rare, this can be fatal (13–17). The incidence of this complication appears to have diminished over the past three decades (10, 18, 19), but nevertheless this remains an important disadvantage of INH therapy. As well, the long duration, and need for close monitoring because of the possibility of serious adverse events, make this regimen relatively costly.

(*Received in original form April 8, 2004; accepted in final form May 30, 2004*)

Supported by a grant from the Medical Research Council of Canada (FRN#44154). Dr. Menzies received a scientist award from the Medical Research Council of Canada and currently holds an FRSQ Chercheur Boursier Senior Award. Dr. Schwartzman holds a Chercheur Boursier Clinicien Award from the FRSQ, and Dr. Brassard holds a New Investigator award from the CIHR.

Correspondence and requests for reprints should be addressed to Dick Menzies, M.D., M.Sc., Montreal Chest Institute, 3650 St-Urbain, Room K1.24, Montreal, PQ, H2X 2P4 Canada. E-mail: dick.menzies@mcgill.ca

Am J Respir Crit Care Med Vol 170. pp 445–449, 2004
Originally Published in Press as DOI: 10.1164/rccm.200404-478OC on June 1, 2004
Internet address: www.atsjournals.org

Because of these problems, there has been considerable interest in finding shorter and better tolerated regimens for the treatment of LTBI (20). In 2000, two alternative regimens were recommended—2 months of daily rifampin and pyrazinamide (2RIF–PZA) and 4 months of daily rifampin (4RIF) (8, 21). After more widespread use, the 2RIF–PZA regimen was associated with serious hepatotoxicity (22–24) and deaths (22, 25). As a result this is now recommended only for carefully selected high-risk individuals such as human immunodeficiency virus (HIV)-infected persons (26), in whom its efficacy and safety have been demonstrated (27). This leaves 4RIF as the only currently recommended alternative to 9INH for treatment of LTBI in the great majority of HIV-negative persons. However, there is little published information regarding treatment completion, safety, or efficacy. In one randomized trial, the efficacy and tolerability of 3 months of rifampin alone were somewhat better than those of 6INH among older Chinese males with pulmonary silicosis (28). In two case series, 6 months of rifampin was well tolerated in homeless persons in Boston (29), and in high school students in California (30).

We have undertaken a single-center randomized trial to test the hypothesis that completion of therapy would be significantly better with 4RIF than with 9INH. We also compared the safety and tolerability of the two regimens. Some results from this study have been presented in abstract form (31).

METHODS

Setting, Study Population, and Randomization

An open-label randomized controlled trial was conducted at a university-affiliated respiratory hospital. Patients were considered eligible if they were 18 years of age or older and had a documented tuberculin skin test that met the criteria for a positive test by Canadian standards (21), and their treating physician initially recommended 9INH for LTBI. Contacts of INH-resistant cases (32) and patients with hypersensitivity to rifamycins or who were taking therapy with potential interactions with rifampin, without any available acceptable alternative (e.g., antiretroviral therapy), or who refused alternatives (e.g., oral contraceptives), were ineligible. Eligible patients who signed informed consent forms were randomized to 4 months of daily RIF (10 mg/kg, up to 600 mg/day) or 9 months of daily INH (5 mg/kg, up to 300 mg/day), using an Internet-accessible computerized program that also verified eligibility. Randomization was stratified by risk of TB (high if patient was HIV infected, had close contacts with active TB, or had fibronodular changes on chest X-ray; and low to moderate for all others), because compliance may be different in these risk groups (33–35).

Randomization of 58 patients per arm provided 80% power to detect significantly better treatment completion with 4RIF ($\alpha = 0.05$ and one-sided test), expecting 70% completion of 9INH, and 90% with 4RIF (36). The study was approved by an ethics committee of the Montreal Chest Institute of the McGill University Health Centre (Montreal, PQ, Canada).

Data Gathering

After randomization, patients were monitored in routine fashion. Liver transaminases and bilirubin were measured pretreatment and after 1 month of therapy in all patients. Patients were seen after 4 weeks of therapy and then every 6 weeks. The treating physician made all

management decisions, including discontinuation of therapy, or testing for drug-induced hepatitis.

The primary outcome was the percentage of prescribed doses taken, measured with an electronic device in the pill container cap, which recorded the date and time of bottle opening (medication event-monitoring system [MEMS] device; Aprex [a division of Aardex], Fremont, CA).

Secondary outcomes included adverse events resulting in permanent discontinuation of therapy. Drug-induced hepatitis was defined as liver transaminase (alanine transaminase) levels more than three times the upper limits of normal with symptoms, or transaminase levels more than five times the upper limits of normal without symptoms (8). Health care system costs were based on health care use after randomization (37). Institutional costs were based on actual costs at the Montreal Chest Institute in 2003, and professional fees on the 2003 reimbursement schedule of the Régie de l'Assurance Maladie du Québec. Medication costs were based on pills dispensed, pharmacist fees, and global TB drug facility prices (38). Costs for the electronic monitors were not included.

Data Analysis

Patients were considered to have completed therapy if they took more than 80% of total prescribed doses within 20 weeks for 4RIF, or 43 weeks for 9INH.

Characteristics of nonparticipants and participants, and of participants randomized to the two arms, were compared on the basis of χ^2 tests for categorical variables, and Student *t* tests for continuous variables (36). Nonparametric tests were used to compare costs between patients randomized to the two arms (36).

RESULTS

Between January 21 and October 1, 2002, 227 patients were recommended to take 9INH for LTBI by their treating physicians and referred to the study for screening. As shown in Figure 1, 18 of those screened were not eligible, and 93 refused. Most of those who refused did so because they were not interested in participating in research, or preferred to take the standard therapy as initially recommended by their treating physician. As shown in Table 1, the characteristics of those who refused and of the patients randomized to the two treatment arms were not significantly different. Information about nonparticipants was limited to that shown in Table 1. However, among participants other characteristics, not shown in Table 1, that were similar in the 9INH and the 4RIF groups included the following: cigarette smoking, alcohol use, time since arrival in Canada (if foreign born), travel to TB-endemic countries, past TB exposure, presence of symptoms, and other medical illnesses including liver and kidney diseases, and hepatitis B and hepatitis C infection.

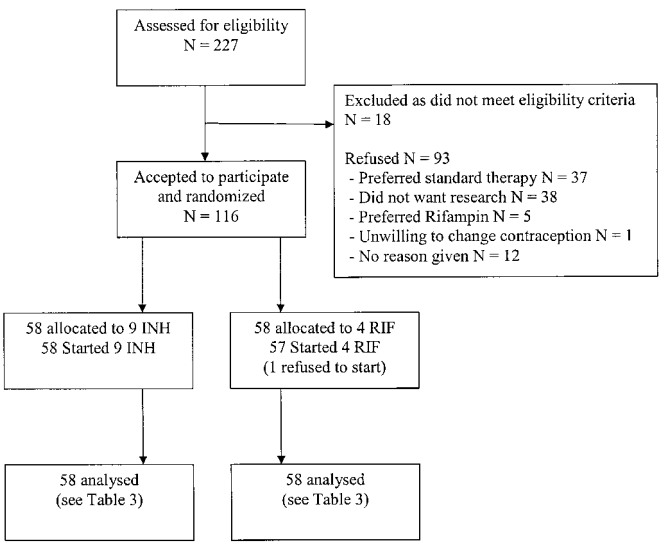

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram: 4 months of rifampin versus 9 months of INH.

As shown in Table 2, of the 58 randomized to 4RIF, 53 (91%) completed therapy, and 50 (86%) took more than 90% of doses within the allowed time, compared with 44 (76%), and 36 (62%), respectively, of patients allocated to 9INH (both differences significant, $p < 0.05$). Major adverse events, resulting in permanent discontinuation of therapy by their treating physician, were somewhat more frequent among patients allocated to 9INH. These events were significantly associated with age over 35 years and a history of liver disease, but were not associated with sex, country of origin, or years since arrival in Canada (data not shown in tabular form). Drug-induced hepatitis developed in three patients, after 74, 105, and 137 doses of isoniazid. None of these three patients had abnormal liver tests before treatment. Conversely, of the eight with baseline abnormal transaminases, none developed hepatitis. Minor symptoms—which did not result in any change of therapy—were similar for the two regimens except for a significantly greater occurrence of fatigue with 4RIF (15 versus 4%, $p < 0.001$).

As seen in Table 3, the proportion of doses taken each month was generally higher with rifampin, although significantly higher

TABLE 1. BASELINE CHARACTERISTICS OF NONPARTICIPANTS AND PATIENTS RANDOMIZED TO THE TWO REGIMENS

	Nonparticipants (*n = 93*)	9-mo INH (*n = 58*)	4-mo RIF (*n = 58*)
Age, mean (SD)	34.2 (10.6)	34.8 (13.0)	32.9 (10.8)
⩽ 35 yr, n (%)	62 (67%)	39 (67%)	41 (71%)
> 35 yr, n (%)	31 (33%)	19 (33%)	17 (29%)
Sex, n (%)			
Female	43 (46%)	29 (50%)	22 (38%)
Male	50 (54%)	29 (50%)	36 (62%)
Country of birth, n (%)			
Canada	7 (8%)	6 (10%)	9 (16%)
Foreign*			
Low TB	0 (0%)	0 (0%)	2 (3%)
Intermediate TB	13 (14%)	4 (7%)	2 (3%)
High TB	73 (78%)	48 (83%)	45 (78%)
Reason for referral, n (%)			
Abnormal CXR	41 (44%)	31 (53%)	29 (50%)
Contact	12 (13%)	10 (17%)	10 (17%)
Screening	41 (38%)	17 (29%)	17 (29%)
TST conversion	2 (2%)	0 (0%)	2 (3%)
Tuberculin skin test, n (%)			
5–9 mm	6 (6%)	3 (5%)	3 (5%)
10–14 mm	25 (27%)	20 (34%)	10 (17%)
15+ mm	62 (67%)	35 (60%)	45 (78%)
History of BCG, n (%)			
Received	§	16 (28%)	12 (21%)
Never		30 (52%)	35 (60%)
Unknown		12 (21%)	11 (19%)
Liver tests, pretreatment†			
Patients with ALT > 45, n (%)	§	3 (5%)	5 (9%)
ALT, mean (SD)		19.2 (14.2)	23.4 (15.4)
Bilirubin, mean (SD)		11.6 (5.1)	12.2 (5.9)

Definition of abbreviations: ALT = alanine transaminase; CXR = chest X-ray; INH = isoniazid; RIF = rifampin; TB = tuberculosis.

None of the differences in proportion or mean values between nonparticipants or the two treatment groups were statistically significant at $p < 0.05$.

Percentage of all patients in each group. Totals may not equal 100% because of rounding.

* Countries classified according to TB incidence as suggested by the World Health Organization (45).

§ This information was not available for nonparticipants.

† Normal ranges: ALT, 6–45 U/L; bilirubin, 1.7–18.9 μmol/L.

TABLE 2. OUTCOMES OF STUDY PARTICIPANTS

	9-mo INH		4-mo RIF		
	n	%	n	%	Relative Risk‡ (95% CI)
Randomized	58		58		
Completed treatment					
Total*	44	76	53	91	1.2 (1.02, 1.4)
Took > 90% of doses	36	62	50	86	1.4 (1.1, 1.7)
Took 80–89% of doses	8	14	3	5	0.4 (0.1, 1.3)
Did not complete					
Total	14	24	5	9	
Dropout/default	6	10	3	5	0.5 (0.1, 1.9)
Serious adverse events†					
Total	8	14	2	3	0.25 (0.1, 1.1)
Hepatitis	3	5	0	0	—

Definition of abbreviation: CI = confidence interval.

* *Completed* defined as took 80% or more of doses within 20 weeks for 4RIF or within 43 weeks for 9INH.

† *Serious adverse events* defined as events that resulted in permanent discontinuation of therapy, by their treating physician. The seven other adverse events were as follows: severe nausea and vomiting in four, persistent debilitating fatigue in two, and rash in one.

‡ Relative risk: calculated as risk of outcome with 4RIF divided by risk of outcome with 9INH.

TABLE 3. COMPLIANCE BY MONTH FOR EACH REGIMEN

	9-mo INH	4-mo RIF	p Value†
Randomized	58	58	
Month 1			
Stopped			
Side effects	3	2	
Dropout	3	1	
No. on treatment at end of Month 1	52	55	
Doses taken during Month 1 for all patients	90.3%	92.1%	NS
Month 2			
Stopped			
Side effects	1	0	
Dropout	1	1	
No. on treatment at end of Month 2	50	54	
Doses taken during Month 2 for patients on treatment at start of Month 2	90.8%	96.8%	0.03
Month 3			
Stopped			
Side effects	1*	0	
Dropout	0	0	
No. on treatment at end of Month 3	49	54	
Doses taken during Month 3 for patients on treatment at start of Month 3	93.5%	96.2%	NS
Month 4			
Stopped			
Side effects	0	0	
Dropout	0	1	
No. on treatment at end of Month 4	49	53	
Doses taken during Month 4 for patients on treatment at start of Month 4	92.3%	93.1%	NS
Month 6			
Stopped			
Side effects	1*	—	
Dropout	0	—	
No. on treatment at end of Month 6	48	—	
Doses taken during Month 6 for patients on treatment at start of Month 6	93.6%	—	
Month 9			
Stopped			
Side effects	2	—	
Dropout	2	—	
No. on treatment at end of Month 9	44	—	
Doses taken during Month 9 for patients on treatment at start of Month 9	91.2%	—	

Doses taken measured by electronic monitoring device (MEMS).

* Occurrence of drug-induced hepatitis.

† p Values for difference in percentage of doses taken: from *t* tests (NS, $p > 0.05$).

only in Month 2. Most dropouts occurred early. Therefore, among the patients remaining on therapy after Month 2, the proportion of doses taken was high.

Overall costs of follow-up were significantly greater for patients allocated to 9INH (Table 4), although the majority of costs were related to routine follow-up visits. No patients were hospitalized during follow-up. Nonroutine costs—for unscheduled clinic visits, consultations, and emergency room visits, and related laboratory investigations—were approximately twice as high per patient randomized to 9INH than to 4RIF.

DISCUSSION

In this study, significantly more patients randomized to 4RIF completed an adequate course of therapy, with significantly lower follow-up costs, and somewhat less frequent major adverse events. This small trial did not have adequate power to assess safety or efficacy. These results should not be interpreted to mean that 4RIF can replace 9INH for routine treatment of latent TB infection.

It may seem obvious that a much shorter regimen should result in better treatment completion. However, in randomized trials completion of 2RIF–PZA was no better than 6INH (23, 39), although it was better than 12INH (27). And in two case series, only 57% (40), or 68% (41), of patients completed the 2RIF–PZA regimen, which cannot be considered optimal. Evaluation of the efficacy of a shorter LTBI regimen is a major undertaking. To initiate this would be justified only if completion of that regimen was significantly better than with the current standard of 9INH. This is why the primary objective of the present study was to assess treatment completion. Having now demonstrated superior completion rates, the next step should be a study with adequate power to evaluate safety. Once this is completed, then a decision can be made to launch a large-scale efficacy study.

An important potential limitation of the study design was the absence of blinding. Awareness of the regimen may have influenced reporting by patients, and recording by providers, of symptoms. The resultant bias may have accounted for the differences seen. Bias also may have influenced decisions by physicians to discontinue therapy permanently. Although drug-induced hepatitis was diagnosed on the basis of objective laboratory measurements, judgment regarding the severity of the other adverse events such as nausea and vomiting, or fatigue, is more subjective, and therefore potentially subject to bias by the treating physician. However, an unblinded study was justified because the primary study outcome—treatment completion—was likely strongly influenced by the duration of therapy. In addition, the results of an unblinded study may be more applicable to routine practice. This also permitted assessment of the impact on patient compliance of the greater number of pills, and discoloration of body fluids of 4RIF.

Patient compliance may have been overestimated, if patient behavior was influenced by the knowledge that every opening of the pill container was recorded electronically. However, this was considered essential to achieve accurate measurement of the primary outcome. It may also be argued that actual ingestion of the medication was not measured, because the electronic device recorded only when the bottle was opened. However, regularity of bottle opening, measured with the same device,

TABLE 4. HEALTH CARE USE AND COSTS IN CANADIAN DOLLARS DURING FOLLOW-UP FOR EACH REGIMEN

		9-mo INH		4-mo RIF	
	Unit Cost (Can$)†	n	Cost (Can$)†	n	Cost (Can$)†
Clinical visits					
Routine*					
MD + RN	56.60	330	18,678	214	12,112
RN only	23.10	28	647	12	277
Unscheduled					
MD + RN	114.35	8	915	2	229
RN only	23.10	5	116	4	92
Phone calls	23.10	2	46	3	69
Emergency room	155.85	1	156	0	0
Consultations (GI, dermatology)	98.00	5	490	0	0
Drug costs (per month)	0.23 (INH) 2.62 (RIF)	439	101	220	576
Pharmacist fees (monthly)	7.00	439	3,073	220	1,540
Laboratory					
Additional chest X-ray	18.50	5	93	4	74
Liver function tests (includes ALT, alkaline phosphatase, bilirubin)	15.25‡	161	2,455	127	1,937
SMA-7 (includes glucose, BUN, creatinine, electrolytes)	11.55	10	116	8	92
Complete blood count (includes WBC, hemoglobin, hematocrit, platelet count)	5.50	9	50	4	22
Hepatitis serology					
Hepatitis B	40.00	1	40	3	120
Hepatitis C	20.00	2	40	2	40
Total costs					
Total costs of follow-up			27,014		17,182
Mean cost per patient allocated			466§		296§
Mean cost per patient completed			614		324
Costs for nonroutine care			1,819		739
Mean cost per patient allocated			31¶		13¶

Definition of abbreviations: BUN = blood urea nitrogen; GI = gastrointestinal; SMA-7 = sequential multiple analyzer-seven; WBC = white blood cell count.

* Routine visits: includes visits at end of therapy.

† $1.00 Canadian = $0.75 U.S. at time of analysis (January 2004).

‡ Includes $7.00 cost for drawing blood samples.

§ $p < 0.0001$ for difference in total costs per patient, based on Wilcoxon rank sum test.

¶ $p = 0.14$ for difference in nonroutine costs, based on Wilcoxon rank sum test.

has been correlated with efficacy of treatment of hyperlipidemia (42) and diabetes (43).

The study had a number of strengths. The process of routine care was disrupted as little as possible, to minimize the effect of participation in a randomized trial, which may itself result in greater patient compliance. As a result the estimates of treatment completion may be more realistic. In support of this, the completion rate of 9INH in this trial fell within the range of previous measures of treatment completion under routine conditions at this hospital, that is, 50–60% with 12INH (33, 34) and 80% with 6INH (35).

In initial randomized trials with INH and 2RIF–PZA, incidence of major adverse events was substantially lower (27, 44) than documented subsequently when prescribed by many providers in routine practice (13, 17, 22, 25). Why incidence has been lower in randomized trials is unknown, but we speculate this may have reflected selection into these trials of persons at lower risk for adverse events. In the present study only patients in whom rifamycins were clearly contraindicated were excluded. By including, as much as possible, all other patients, the estimates of adverse events and compliance should be more realistic and relevant to routine practice. For example, this was why patients with abnormal baseline lung function tests were considered eligible for this trial. In these patients the decision to prescribe 9INH was made without consideration of this trial, by the treating physician who had judged that the benefits of treatment outweighed the increased risks. Only after this clinical decision had been made, and discussed with the patients, were they considered eligible for this trial. This method of recruitment may explain why a substantial number of eligible subjects refused. However, their demographic and clinical characteristics were similar to those of the participants, reducing the likelihood that nonparticipation caused bias in the estimates of compliance and adverse events.

The results of this study confirm that patient acceptance and compliance with 4RIF are excellent. The next step is a trial with adequate power to assess safety and tolerability in a group of patients representative of those likely to receive this therapy in future. Some may argue that the safety and tolerability of rifampin is well known from treatment of millions of persons with active TB. However, a similar assumption proved incorrect for the 2RIF–PZA regimen—once introduced widely into clinical practice for treatment of LTBI, it was associated with unacceptable rates of hepatotoxicity and death. Therefore a careful assessment of the safety of the 4RIF regimen is needed before undertaking an efficacy study. If the safety and tolerability of 4RIF are equivalent to or better than those of 9INH, then a large-scale efficacy study would be justified.

Conflict of Interest Statement: D.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.-J.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; B.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; S.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; P.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; K.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Acknowledgment: The authors thank the staff of the tuberculosis clinic, particularly Jen Lee, Isabelle Parisien, Isabelle Rocher, and Denis Francis.

References

1. Moulding T. Chemoprophylaxis of tuberculosis: when is the benefit worth the risk and cost? *Ann Intern Med* 1971;74:761–770.
2. Jordan TJ, Lewitt EM, Reichman LB. Isoniazid preventative therapy for tuberculosis: decision analysis considering ethnicity and gender. *Am Rev Respir Dis* 1991;144:1357–1360.
3. Jordan TJ, Lewit EM, Montgomery RL, Reichman LB. Isoniazid as preventive therapy in HIV-infected intravenous drug abusers: a decision analysis. *JAMA* 1991;265:2987–2991.
4. Mohle-Boetani JC, Miller B, Halpern M, Trivedi A, Lessler J, Solomon SL, Fenstersheib M. School-based screening for tuberculous infection: a cost–benefit analysis. *JAMA* 1995;274:613–619.
5. Khan K, Muennig P, Behta M, Pharm D, Zivin JG. Global drug-resistance patterns and the management of latent tuberculosis infection in immigrants to the United States. *N Engl J Med* 2002;347:1850–1859.
6. Jasmer RM, Nahid P, Hopewell PC. Latent tuberculosis infection. *N Engl J Med* 2002;347:1860–1866.
7. Salpeter SR, Sanders GD, Salpeter EE, Owens DK. Monitored isoniazid prophylaxis for low-risk tuberculin reactors older than 35 years of age: a risk–benefit and cost–effectiveness analysis. *Ann Intern Med* 1997; 127:1051–1061.
8. American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000;161: S221–S247.
9. Comstock GM. How much isoniazid is needed for prevention of tuberculosis in immunocompetent adults. *Int J Tuberc Lung Dis* 1999;3:847–850.
10. Nolan CM, Goldberg SV, Buskin SE. Hepatoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. *JAMA* 1999;281:1014–1018.
11. LoBue PA, Moser KS. Use of isoniazid for latent tuberculosis infection in a public health clinic. *Am J Respir Crit Care Med* 2003;168:443–447.
12. Dash LA, Comstock GW, Flynn JPG. Isoniazid preventive therapy. *Am Rev Respir Dis* 1980;121:1039–1044.
13. Garibaldi RA, Drustin RE, Ferebee SH, Gregg MB. Isoniazid-associated hepatitis. *Am Rev Respir Dis* 1972;106:357–365.
14. Maddrey WC, Boitnott JK. Isoniazid hepatitis. *Ann Intern Med* 1973;79: 1–12.
15. Meyers BR, Halpern M, Sheiner P, Mendelson MH, Miller C, Schwartz M, Mor E. Acute hepatic failure in seven patients after prophylaxis and therapy with antituberculosis agents. *Transplantation* 1994;58:372–376.
16. Black M, Mitchell JR, Zimmerman HJ, Ishak KG, Epler GR. Liver physiology and disease: isoniazid-associated hepatitis in 114 patients. *Gastroenterology* 1975;69:289–302.
17. Kopanoff DE, Snider D, Caras GJ. Isoniazid-related hepatitis. *Am Rev Respir Dis* 1978;117:991–1001.
18. Snider D, Caras GJ. Isoniazid-associated hepatitis deaths: a review of available information. *Am Rev Respir Dis* 1992;145:494–497.
19. Salpeter SR. Fatal isoniazid-induced hepatitis: its risk during chemoprophylaxis. *West J Med* 1993;159:560–564.
20. Jasmer RM, Daley CL. Rifampin and pyrazinamide for treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2003;167:809–812.
21. Long R. Canadian tuberculosis standards, 2000/2001 ed. Toronto, Canada: Canadian Lung Association; 2000. p. 1–251.
22. American Thoracic Society, Centers for Disease Control and Prevention. Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in the American Thoracic Society/CDC recommendations. *MMWR Morb Mortal Wkly Rep* 2001;50:733–735.
23. Jasmer RM, Saukkonen JJ, Blumberg HM, Daley CL, Bernardo J, Vittinghoff E, King MD, Kawamura LM, Hopewell PC. Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. *Ann Intern Med* 2002;137:640–647.
24. Kunimoto D, Warman A, Beckon A, Doering D, Lelenka L. Severe hepatotoxicity associated with rifampin–pyrazinamide preventative therapy requiring transplantation in an individual at low risk for hepatotoxicity. *Clin Infect Dis* 2003;36:e158–e161.
25. Centers for Disease Control and Prevention. Fatal and severe hepatitis associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection: New York and Georgia, 2000. *MMWR Morb Mortal Wkly Rep* 2001;50:289–291.
26. American Thoracic Society, Centers for Disease Control and Prevention. Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection–United States, 2003. *MMWR Morb Mortal Wkly Rep* 2003;52:735–739.
27. Gordin F, Chaisson RE, Matts JP, Miller C, de Lourdes Garcia M, Hafner R, Valdespino JL, Coberly J, Schechter M, Klukowicz AJ, Barry MA, O'Brien RJ. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons. *JAMA* 2000;283:1445–1450.
28. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. *Am Rev Respir Dis* 1992;145:36–41.
29. Polesky A, Farber HW, Gottlieb DJ, Park H, Levinson S, O'Connell JJ, McInnis B, Nieves RL, Bernardo J. Rifampin preventative therapy for tuberculosis in Boston's homeless. *Am J Respir Crit Care Med* 1996; 154:1473–1477.
30. Villarino ME, Ridzon R, Weismuller PC, Elcock M, Maxwell RM, Meador J, Smith PJ, Carson ML, Geiter LJ. Rifampin preventive therapy for tuberculosis infection: experience with 157 adolescents. *Am J Respir Crit Care Med* 1997;155:1735–1738.
31. Dion MJ, Behr M, Bourbeau J, Collet JP, Brassard P, Schwartzman K, Tannenbaum T, Menzies D. Randomised clinical trial comparing 9 months isoniazid to 4 months rifampin for the treatment of latent TB infection: preliminary report [abstract]. *Am J Respir Crit Care Med* 2003; 167;A433.
32. Nolan CM, Aitken ML, Elarth AM, Anderson KM, Miller WT. Active tuberculosis after isoniazid chemoprophylaxis of Southeast Asian refugees. *Am Rev Respir Dis* 1986;133:431–436.
33. Menzies RI, Rocher I, Vissandjee B. Factors associated with compliance in treatment of tuberculosis. *Tuber Lung Dis* 1993;74:32–37.
34. Adhikari N, Menzies R. Community-based tuberculin screening in Montreal: a cost–outcome description. *Am J Public Health* 1995;85:786–790.
35. Dasgupta K, Schwartzman K, Marchand R, Tannenbaum TN, Brassard P, Menzies D. Comparison of cost effectiveness of tuberculosis screening of close contacts and foreign-born populations. *Am J Respir Crit Care Med* 2000;162:2079–2086.
36. Dawson-Saunders B, Trapp RG. Basic and clinical biostatistics. Norwalk, CT: Appleton & Lange; 1990.
37. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes, 2nd ed. New York: Oxford University Press; 1997.
38. Global Drug Facility. First-line tuberculosis drugs & formulations currently supplied/to be supplied by the global TB drug facility. November 22, 2003. URL: http://stoptb.org/GDF/drugsupply/drugs.available.html.
39. Geiter LJ. Results of a randomized, controlled trial to assess the toxicity and patient adherence with two short-course regimens for the prevention of tuberculosis in a a two-month regimen of rifampin and pyrazinamide or a four-month regimen of rifampin only, in comparison with a control regimen of six months-isoniazid. Ph.D. thesis. Baltimore, MD: Epidemiology Department, School of Hygiene and Sanitation, Johns Hopkins University; 1997.
40. Lee AM, Mennone JZ, Jones RC, Paul WS. Risk factors for hepatotoxicity associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection: experience from three public health tuberculosis clinics. *Int J Tuberc Lung Dis* 2002;6:995–1000.
41. Stout JE, Engemann JJ, Cheng AC, Fortnberry ER, Hamilton CD. Safety of 2 months of rifampin and pyrazinamide for treatment of latent tuberculosis. *Am J Respir Crit Care Med* 2003;167:824–827.
42. Schwed A, Fallab CL, Burnier M, Waeber B, Kappenberger L, Burnand B, Darioli R. Electronic monitoring of compliance to lipid-lowering therapy in clinical practice. *J Clin Pharmacol* 1999;39:402–409.
43. Mason BJ, Matsuyama JR, Jue SG. Assessment of sulfonylurea adherence and metabolic control. *Diabetes Educ* 1995;21:52–57.
44. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. *Adv Tuberc Res* 1969;17:28–106.
45. World Health Organization, Global Tuberculosis Programme. Global tuberculosis control: WHO report 1998. Geneva, Switzerland: World Health Organization; 1998.