

# Four-Month, Four-Drug Preventive Therapy for Inactive Pulmonary Tuberculosis

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Standard preventive therapy for inactive pulmonary tuberculosis (TB) is 12 mo of isoniazid. Shorter multiple-drug preventive regimens have been proposed. From December 1993 through January 1996 we evaluated a 4-mo, four-drug regimen of preventive therapy for patients with inactive TB, mostly newly arriving immigrants from countries with high rates of TB and of isoniazid resistance. Fifty-three evaluable patients received a 4-mo regimen of isoniazid, rifampin, ethambutol, and pyrazinamide. We compared their completion rate, side effects, and cost of treatment with those of 108 age-matched patients who had received 12 mo of isoniazid at an earlier time. Sixty-eight percent of patients on the 4-mo regimen completed treatment; 69% of those on the 12-mo regimen completed treatment ( $p = 0.9393$ ). Side effects were more frequent for the 4-mo regimen (30.2%) compared with 12 mo of isoniazid (11.1%) ( $p = 0.0027$ ). The cost of providing an uncomplicated, self-supervised regimen was estimated to be almost four times greater for the four-drug regimen compared with isoniazid. These results show that, in terms of compliance, a four-drug, 4-mo regimen had no advantage over standard preventive therapy for persons with inactive pulmonary TB. On the other hand, the shorter, more intensive regimen was associated with more frequent adverse effects and was more costly. Goldberg SV, Duchin JS, Shields T, Nolan CM. Four-month, four-drug preventive therapy for inactive pulmonary tuberculosis.

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Inactive pulmonary tuberculosis (TB) is defined as the presence of "abnormal stable radiographic findings in a person with a positive reaction to tuberculin skin test, negative bacteriologic studies (if done), and no clinical and/or radiographic evidence of current disease" (1). Persons with inactive pulmonary TB have an annual risk of developing active disease that is at least two and a half times greater than the risk of those with latent tuberculous infection with no pulmonary abnormalities (2). The rate of progression from inactive pulmonary TB to active disease is exceeded only by the activation rates for recently infected contacts of infectious cases of TB (3-6), persons with silicosis and TB infection (7), and individuals coinfecting with human immunodeficiency virus (HIV) and TB (8). Patients with inactive pulmonary TB are therefore among the highest priority groups for preventive therapy (9).

Standard advice for many years has been to offer patients with inactive pulmonary TB a year of isoniazid preventive therapy (10, 11). Clinical trials have demonstrated protection rates of 60% to 90% (2, 5, 12, 13). However, data from public health programs in recent years have shown completion rates of isoniazid preventive therapy to be only about 60% (14). Most authorities believe that an equally safe and effective reg-

imen of shorter duration would be completed by more patients and therefore would be of greater benefit to patients and to society.

In 1994, the American Thoracic Society and the Centers for Disease Control and Prevention (ATS-CDC) jointly recommended a regimen of 4 mo of isoniazid and rifampin as acceptable chemotherapy for sputum smear- and culture-negative TB (9). That statement also suggests that 4 mo of isoniazid and rifampin is an acceptable alternative to 12 mo of isoniazid for patients with inactive pulmonary TB and those with silicosis, if the risk of isoniazid resistance is low.

In 1993, in anticipation of the new ATS/CDC recommendations previously described, we undertook a preliminary evaluation of 4-mo preventive therapy for recently arrived immigrants who are determined during their overseas visa application process to have inactive pulmonary TB ("Class B"). Because program data show rates of isoniazid resistance of 10 to 20% in cases of active TB from those populations (15), we chose a multiple-drug regimen of isoniazid, rifampin, pyrazinamide, and ethambutol for the full 4-mo duration of treatment. That regimen was chosen because of success with a four-drug regimen in the treatment of culture-negative TB in similar populations in British Medical Research Council clinical trials (16), and lack of data on the efficacy of less intensive regimens for inactive TB in populations with a relatively high rate of isoniazid resistance.

Finally, we conducted a retrospective cohort study of completion and toxicity of this new short-course preventive regimen for persons at risk of isoniazid resistance, using a matched group of historical cases who had received the 12-mo isoniazid preventive therapy regimen.

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TABLE 1  
DEMOGRAPHIC AND DIAGNOSTIC DATA FOR STUDY  
PATIENTS WITH INACTIVE PULMONARY TUBERCULOSIS

Variable	Four-drug Group n (%)	Isoniazid Group n (%)
Number	53 (33)	108 (67)
Age, yr, mean $\pm$ SD	47.2 $\pm$ 15.0	49.7 $\pm$ 16.7
Male	37 (70)	58 (54) $p = 0.0508$
PPD		
0-4 mm	0 (0)	0 (0)
5-9 mm	2 (4)	3 (3)
10-14 mm	24 (45)	45 (42)
$\geq$ 15 mm	27 (51)	60 (56)
Country of origin		
Philippines	14 (26)	40 (37)
Vietnam	19 (36)	52 (48)
China, Hong Kong	9 (17)	8 (7)
Other	11 (21)	8 (7) $p = 0.0136$
Race		
White	2 (3.8)	1 (0.9)
Black	3 (5.7)	1 (0.9)
American Indian	1 (1.9)	1 (0.9)
Asian-Pacific Islander	47 (88.7)	105 (97.2)
English-speaking	26 (49)	43 (40)
Bilateral chest X-ray abnormality	29 (55)	30 (28) $p = 0.0009$

## METHODS

From December 1993 through September 1995, Class B-TB immigrants who came to the Seattle-King County Department of Public Health (SKCDPH) TB Clinic were evaluated by means of a tuberculin skin test, chest roentgenogram, clinical interview, and at least two sputum cultures. Those who were initially determined to have inactive TB and who were considered candidates for preventive therapy were placed on the four-drug regimen, isoniazid 300 mg, rifampin 600 mg, pyrazinamide 15 to 30 mg/kg, and ethambutol 15 mg/kg, daily and mostly self-supervised, for the entire 4 mo. Those who were suspected on the basis of that evaluation to have active TB were placed on four-drug directly observed therapy (DOT) and excluded from the present study. Patients with chest X-ray findings suggestive of inactive TB who had strong evidence of previous adequate treatment and those who had negative two-step skin tests and were neither anergic nor HIV-infected, were dismissed from further TB clinic follow-up.

During the period of study, 59 patients were evaluated and were initially thought to have inactive pulmonary TB. Six (10%) of these were determined to have active TB on the basis of positive cultures or on clinical grounds and were excluded from further analysis. Fifty-three evaluable patients were thus entered in the four-drug group. Nine patients (17%) received all or part of the four-drug regimen by DOT. Forty-four patients (83%) received the drugs with self-supervision.

A historical cohort of Class B patients was chosen by review of clinic logs and charts of patients started on the 12-mo regimen of isoniazid from 1991 through 1993. These logs and charts were searched manually to find two historical, isoniazid-treated patients for each four-drug patient, matching for age within 5 yr. During that period of time Class B-TB immigrants were screened with tuberculin testing, chest X-ray, and clinical interview. Patients who were determined on

TABLE 2  
COMPLETION RATES

Definition of Completion	Four-drug Group n (%)	Isoniazid Group n (%)	Relative Risk* (95% Confidence Intervals)
85% of each regimen	36 (68)	74 (69)	1.1 (0.5, 2.4)
100% of each regimen	35 (66)	69 (64)	1.3 (0.6, 2.6)

\* The relative risk is reported adjusted for race because only that variable was found to confound the comparison of completion between the two regimens.

the basis of these tests to have untreated inactive pulmonary TB were started on a 12-mo course of isoniazid, 300 mg/d (11).

A course of treatment was considered complete if a patient took 85% of the prescribed medication (3.5 mo of the four-drug regimen or 10.5 mo of isoniazid). Analysis was also performed for completion of 100% of each prescribed regimen. Reasons for not completing therapy included loss to follow-up, such as due to patient move or death, medical indications, and noncompliance. Noncompliance was defined by missed appointments, delayed refills, missed doses of medications, and by the clinical decision to change treatment from self-administered to DOT.

Side effects were determined by chart review of monthly symptom checks, unscheduled drop-in clinic visits, and telephone contacts. Side effects were considered most significant if they led to withholding on a temporary basis or discontinuing one or more drugs. The monthly evaluations were performed by experienced TB-control nurses, who followed standard guidelines, checking for side effects relevant to each patient's specific drug regimen (9, 11). The nurses reported significant findings to clinic physicians who determined how to respond to each finding.

Data were abstracted by retrospective chart review and entered into an Epi Info (Version 6.0; CDC, Atlanta, GA) questionnaire. Relative risks were estimated by odds ratios obtained from logistic regression analysis using SPSS software (SPSS Inc., Chicago, IL) (17). The risk of side effects, completion of 85% of treatment, and completion of 100% of treatment for the four-drug group compared with the isoniazid group are presented.

In the model for each outcome, risk factors for completion and side effects were assessed as confounders and retained if they changed the estimate of the relative risk associated with the four-drug regimen by more than 10%. Variables assessed as potential confounders included age, race, gender, English proficiency, symptoms of TB, smoking, alcohol use, chest X-ray findings, and whether treatment was self-supervised or by DOT. The impact of homelessness, incarceration, past medical history, and other drug use could not be assessed because of insufficient numbers.

Patients who moved may be considered not to have completed treatment. However, many patients who move transfer their medical care as well, usually encouraged by an official interstate TB control transfer of information, and may complete TB preventive therapy in another jurisdiction. Completion and side effect analyses were therefore performed twice: once including those who moved as persons not completing therapy and once excluding those who moved from the analysis. These results were then compared.

Cost of treatment was estimated by adding the average wholesale price for the drugs used, estimated actual lab cost of performing standard sputum smears and cultures, and the Medicaid maximum allowable billable fees for clinical services in Washington State.

TABLE 3  
SIDE EFFECTS AMONG PATIENTS ON FOUR-DRUG,  
4-mo AND 12-mo ISONIAZID PREVENTIVE THERAPY

Finding	Four-Drug Group n (%)	Isoniazid Group n (%)	p Value
Any side effects	16 (30.2)	12 (11.1)	0.027*
Side effects treated	7 (13.2)	4 (3.8)	0.1238
Treatment withheld due to side effects	15 (28.3)	8 (7.4)	0.0004
Treatment discontinued due to side effects	6 (11.3)	5 (4.6)	0.180
Side effect			
Headache	1 (1.9)	1 (0.9)	0.5514
Nausea and vomiting	4 (7.5)	1 (0.9)	0.0407
Abdominal pain	1 (1.9)	1 (0.9)	0.5514
Vision changes	6 (11.3)	0 (0)	0.0010
Itch	1 (1.9)	2 (1.9)	1.0
Rash	4 (7.5)	4 (3.7)	0.4407
Other	7 (13.2)	5 (4.5)	0.0619

\* Relative risk, adjusted for gender = 4.2; 95% confidence intervals: 1.7, 10.2.

TABLE 4  
COST ESTIMATES FOR TREATMENT WITH FOUR-DRUG,  
4-mo AND 12-mo ISONIAZID PREVENTIVE THERAPY

Item	Isoniazid, 12 mo			Four Drugs, 4 mo		
	Unit Cost	n	Total	Unit Cost	n	Total
Initial clinic visit*	\$33.26	1	\$33.26	\$33.26	1	\$33.26
Tuberculin skin test*	6.05	1	6.05	6.05	1	6.05
Chest X-ray*	16.70	2	33.40	16.70	2	33.40
Blood draw for baseline liver function tests*	2.26	0	0	2.26	1	2.26
Follow-up clinic visit*	19.82	12	237.84	19.82	4	79.28
		104 <sup>§</sup>	2,061.28		80 <sup>§</sup>	1,585.60
Sputum smear and culture <sup>†</sup>	45.00	3	135.00	45.00	3	135.00
Drug cost <sup>‡</sup>	2.61	12	31.32	360.30	4	1,441.20
Total, self-supervised			\$476.87			\$1,730.45
Total, DOT			\$2,300.31			\$3,236.77

\* Maximum billable fee allowed by Washington State Department of Social and Health Services (Reference 30).

<sup>†</sup> Estimated actual laboratory cost of performing standard acid-fast bacilli (AFB) smears and cultures on three sputum specimens.

<sup>‡</sup> Average wholesale price for medications based on dosages for a 140-lb person. Drug Topics Redbook 1998. Medical Economics Company.

<sup>§</sup> Directly observed therapy outreach visits, 5 d/wk for 4 mo for the four-drug regimen; 2 d/wk for 12 mo of isoniazid.

## RESULTS

Among the group receiving four drugs, the mean age was 47.2 yr. 70% were male, 36% were from Vietnam, 26% were from the Philippines, 17% were from China or Hong Kong, and 21% were from other foreign countries (Table 1). Forty-nine percent spoke English with at least some degree of fluency; 96% had purified protein derivative (PPD) skin-test readings  $\geq 10$  mm, and 55% had bilateral chest X-ray abnormalities.

Thirty-six (68%) patients taking the 4-mo regimen completed treatment (Table 2). Only one of these patients did not also go on to complete 100% of the regimen. Sixteen (30.2%) of the four-drug group experienced side effects of their medication (Table 3); 15 (28.3%) had one or more drugs withheld at least temporarily because of side effects; six (11.3%) had one or more medications discontinued because of side effects. The most common side effect was vision changes, 11.3%, followed by nausea and vomiting, 7.5%, and rash, 7.5%.

A total of 108 patients who had been treated with isoniazid for 12 mo from 1991 to 1993 were selected as age-matched historical cases. The 4-mo and 12-mo groups were similar in most demographic and clinical respects, although more 4 mo patients were male and more of this group had bilateral chest X-ray abnormalities (Table 1).

Patients taking the 4-mo regimen were no more likely to complete 85% of prescribed doses than were subjects taking 12 mo of isoniazid (Table 2). Even when completion was defined as taking 100% of prescribed doses, patients taking the 4-mo regimen were not significantly more likely to finish. The results were not significantly different when those who moved were excluded from the analysis.

The four-drug group experienced more side effects than did the isoniazid group, after adjustment for gender (Table 3). The largest difference was in changes in vision. A difference was also noted in the rates of withholding part of the drug treatment because of side effects: 28% of the four-drug group compared with 7.4% of the isoniazid group ( $p = 0.0004$ ). There was not a significant difference in the rates of discontinuing treatment.

Ethambutol was permanently discontinued because of proven or possible changes in vision for six patients, after 1 to 3 mo on four-drug therapy. One patient had clear subjective and objective changes in visual acuity that improved off etham-

butol. Three had only subjective loss of acuity with subsequent improvement. One appeared to lose color discrimination, with no clear subsequent improvement, but later described baseline color blindness that may not have been appreciated at the first examination. The sixth patient had only one eye, and that one impaired, to begin with, and subsequent variable subjective and objective acuity findings, as well as barriers of language and culture that made assessment difficult; his ethambutol was stopped at 1 mo.

The estimated cost of an uncomplicated regimen is greater for the four-drug regimen, \$1,730, compared with the isoniazid regimen, \$477 (Table 4). The four-drug, 4-mo cost doubles, to \$3,237, if daily follow-up visits are made for DOT. The isoniazid regimen would cost \$2,300 if it were given as a 900 mg biweekly DOT regimen.

## DISCUSSION

The striking finding of this study is the lack of difference in completion rates between the two methods of treatment of inactive pulmonary TB. Intuitively, one might think that a much shorter course of medicine would be easier to complete. Our findings do not support that hypothesis. Furthermore, the rate of side effects was greater in the four-drug group, and the shorter regimen was almost four times more costly than 12-mo isoniazid treatment.

The largest difference in side effects was found in vision changes ascribed to ethambutol. The most important toxicity of ethambutol, optic neuritis, is dose-related and is very uncommon at current doses of 15 mg/kg (18). It is possible that if Snellen chart examinations had been performed on the isoniazid group a significant rate of abnormalities would have also been found. The likelihood of this possibility is supported by the finding of Doster and coworkers that decreases in visual acuity were as frequent among TB patients treated without ethambutol (8.3%) as they were among those treated with ethambutol (6.8%) (18).

The 11.3% rate of vision changes in our four-drug group is higher than the rates described during treatment of active disease (18). This may be a result of the longer duration of ethambutol treatment on the four-drug regimen compared with the usual duration of 1 or 2 mo for most patients who are

found to have drug-susceptible tuberculosis. It may also be due to a greater sensitivity on the clinician's part to the risk of causing side effects with a preventive regimen. The bias of a clinician during treatment for disease, with a drug that is known to be well-tolerated, may be to require a high standard of evidence that a drug is causing toxicity before withholding or stopping it, especially if the alternative regimens are known to be more toxic and to require a longer duration of treatment. During preventive therapy, clinicians may have an increased readiness to describe a finding as a possible side effect and to stop the implicated medication.

Our cost comparisons of the two regimens (Table 4) are likely to underestimate the actual cost to the clinic for a four-drug follow-up visit. This is because screening and counseling for side effects for a patient on four drugs require much more nurse and interpreter time than do the same services for a patient on one drug, even though the fee is the same for a follow-up visit whether a patient is on one drug or four drugs. Extra costs that are not part of the present estimate include extra clinic visits, phone calls, and treatments required because of side effects and interpreter time.

A 4-mo preventive regimen of isoniazid and rifampin alone, such as that used by Dutt and coworkers for patients from Arkansas with culture-negative TB (19), would have the advantage of avoiding side effects attributable to pyrazinamide and ethambutol, leading to lower costs and probably, to higher completion rates. That study, however, was performed on a population with a very low rate of isoniazid-resistant TB.

On the other hand, a four-drug regimen of isoniazid, rifampin, pyrazinamide, and streptomycin was successfully used to treat smear-negative, culture-positive cases as well as culture-negative cases of active TB in Hong Kong, where the rate of isoniazid resistance was 8% (16). We chose that regimen, substituting ethambutol for streptomycin, to evaluate for preventive therapy for our Class B-TB patients, who are drawn from populations that have similar or higher rates of isoniazid-resistant tuberculosis. Immigrants from Vietnam, the Philippines, and China, the three largest groups in the present study, who are diagnosed to have active TB in the United States, have been found to have isoniazid resistance rates of 18.3%, 14.7%, and 11.7%, respectively (20).

There is an alternative method of evaluating and treating recently arrived Class B-TB immigrants. Recent studies indicate that 3 to 14% of Class B-TB immigrants have culture-positive TB (21–23) at the time of their initial evaluation in the U.S. Thus, for those who have borderline symptoms or chest X-ray findings that do not clearly establish whether they have inactive or active pulmonary tuberculosis, initiation of a potentially curative, four-drug treatment regimen may be prudent, while sputum stains and cultures are pending. This approach would prevent clinical progression and reduce the potential for transmission of TB for those who are culture-positive. On the other hand, if the cultures are reported negative at the end of 2 mo, the patient will already have had 2 mo of multidrug therapy that can be applied to the total duration of a preventive regimen. For the latter group of patients, two more months of treatment with isoniazid and rifampin may be adequate to prevent future activation. That regimen, isoniazid, rifampin, pyrazinamide, and ethambutol for 2 mo, followed by isoniazid and rifampin for 2 mo, is now being used by several public health TB programs (24).

There are two major limitations to the present study. First, it was designed only to evaluate the safety and compliance, not the efficacy, of the multiple-drug short-course regimen in comparison with 12 mo of isoniazid. The evaluation of efficacy of a new TB preventive therapy regimen in a properly designed

clinical trial will require a major commitment of resources to enroll a large number of patients for an extended period of study and follow-up (2).

Second, the study was conducted essentially as a retrospective chart review of two cohorts, treated sequentially. It is possible that different findings between the two cohorts may relate to their being treated in sequence and that changes in clinic staff, protocols, or attitudes may have had some unexpected effect. We suspect, however, that any bias would have been in favor of the four-drug cohort, because the new approach to preventive therapy among persons with inactive pulmonary TB was undertaken with an intention to make it successful as our new model, following ATS/CDC recommendations (9).

Studies of shorter courses of preventive therapy were called for in the 1989 national strategic plan for the elimination of TB (25). Several such studies have been presented recently for HIV-infected patients (26–28). Those studies have provided the basis for new recommendations for a 2-mo course of rifampin and pyrazinamide as preventive therapy for persons coinfecting with HIV and TB (29). It remains to be determined whether that regimen would also be effective for persons with inactive pulmonary TB.

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