

# Primary Prevention and Treatment of Latent Tuberculosis Infection With Isoniazid: Efficacy of a Control Program, 1997-2002

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**OBJECTIVE:** To analyze the efficacy of a specific program for the study and follow up of tuberculosis contacts. To study factors related to low adherence to treatment and to the development of liver toxicity caused by isoniazid.

**PATIENTS AND METHODS:** Between December 1996 and December 2002, we found 458 contacts of 79 cases of pulmonary tuberculosis in patients uninfected by human immunodeficiency virus. The contacts were screened for tuberculosis infection and chemoprophylaxis was prescribed according to the recommendations of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR).

**RESULTS:** We identified 3 cases of tuberculosis among the contacts (prevalence 0.8%). Chemoprophylaxis with isoniazid was prescribed for 215 contacts. One hundred sixty-nine (79%) completed the prophylaxis protocol. The rate of adherence to treatment was lower in immigrants than in nonimmigrants (odds ratio, 3.42; 95% confidence interval, 1.03-11.04;  $P=0.02$ ). Forty-three patients (22%) developed liver toxicity during treatment, which had to be suspended in 3 cases. Duration of chemoprophylaxis was the only independent variable associated with liver toxicity (odds ratio, 3.80; 95% confidence interval, 1.10-13.13;  $P=0.03$ ).

**CONCLUSIONS:** Our study demonstrates the effectiveness of a specific program of study and follow up of tuberculosis contacts. Immigrants require tailored strategies to improve their adherence to the program. The duration of chemoprophylaxis plays an important role in the development of liver toxicity.

**Key words:** Contact study. Chemoprophylaxis. Latent tuberculosis infection. Isoniazid. Liver toxicity.

Prevención primaria y tratamiento de la infección tuberculosa latente con isoniácida: eficacia de un programa de control, 1997-2002

**OBJETIVO:** Analizar la eficacia de un programa específico para el estudio y seguimiento de los contactos de los pacientes con tuberculosis. Evaluar los factores relacionados con una baja adherencia al tratamiento y con el desarrollo de toxicidad hepática por isoniácida.

**PACIENTES Y MÉTODOS:** Entre diciembre de 1996 y diciembre de 2002 se censaron 458 contactos de 79 casos de tuberculosis pulmonar en pacientes sin infección por el virus de la inmunodeficiencia humana. Se realizó cribado de infección tuberculosa y se indicó quimioprofilaxis según la normativa vigente de la Sociedad Española de Neumología y Cirugía Torácica.

**RESULTADOS:** Encontramos 3 casos de tuberculosis entre los contactos (prevalencia del 0,8%). Se indicó quimioprofilaxis con isoniácida en 215 casos. Un total de 169 (79%) completaron el protocolo de quimioprofilaxis. Los inmigrantes mostraron baja adherencia al tratamiento frente a los que no lo eran (odds ratio = 3,42; intervalo de confianza del 95%, 1,03-11,04;  $p = 0,02$ ). Cuarenta y tres (22%) pacientes presentaron toxicidad hepática durante el tratamiento y en 3 de los casos tuvo que suspenderse. Sólo la duración de la quimioprofilaxis se asoció de forma independiente con el desarrollo de hepatotoxicidad (odds ratio = 3,80; intervalo de confianza del 95%, 1,10-13,13;  $p = 0,03$ ).

**CONCLUSIONES:** Nuestro estudio demuestra la efectividad de un programa específico de estudio y seguimiento de los contactos de pacientes con tuberculosis. Los inmigrantes requieren estrategias individuales para mejorar su adherencia al programa. La duración de la quimioprofilaxis es un factor importante en el desarrollo de hepatotoxicidad.

**Palabras clave:** Estudio de contactos. Quimioprofilaxis. Infección tuberculosa latente. Isoniacida. Hepatotoxicidad.

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## Introduction

Contact studies of persons who live with or maintain stable relations with tuberculosis patients are of great importance in programs for controlling the disease. Through contact studies the epidemiological chain of infection can be broken as new cases and instances of

tuberculosis infection are detected.<sup>1</sup> Between 3% and 6% of contacts will present active disease at the time the study is carried out and more than 50% of those who live with bacilliferous patients will be infected and require chemoprophylaxis.<sup>2,3</sup> Nearly all autonomous communities in Spain have tuberculosis disease control programs underway,<sup>4</sup> demonstrating the interest felt in improving the epidemiological situation. However, there is evident lack of follow-up information about the treatment of both patients and their contacts.

Isoniazid was first recommended for tuberculosis chemoprophylaxis during the 1960s<sup>5</sup> and now, after nearly 50 years of continuous use throughout the world, it continues to be the drug of choice.<sup>6</sup> However, from the start its use has been limited by 2 circumstances: liver toxicity<sup>7,8</sup> and poor adherence to prolonged treatment, which ranges from 6 to 9 months.<sup>9</sup>

The aim of the present study was to evaluate the efficacy of an outpatient clinic dedicated to conventional contact studies of patients with tuberculosis, to the primary prevention of the disease, and to the treatment of tuberculosis infection as part of a control program. A second objective was to identify factors that influence adherence to prescribed treatment and analyze the safety and tolerance of the isoniazid protocol in the primary prevention and treatment of tuberculosis infection.

## Patients and Methods

### Setting

The study was carried out at Hospital Marina Baixa, a 300-bed facility in Public Health Care Area 15 of the Autonomous Community of Valencia (mean population 126000 inhabitants over the study period). Among persons not infected by human immunodeficiency virus (HIV), the tuberculosis incidence rate is 15.8 cases/100 000 population; the rate of sputum-positive diagnoses is 10.41 cases/100000 population. A clinic was held for the purpose of carrying out the program twice per month for 3 hours. A pneumologist and a nurse trained to perform and read tuberculin tests were in attendance.

### Subjects

Following a system of concentric circles,<sup>10</sup> we sought the contacts of HIV negative patients diagnosed with pulmonary tuberculosis (stain- or culture-positive) in our public health care area from December 1996 to December 2002. Contacts younger than 10 years old were referred to the pediatric clinic.

### Clinical Study and Tuberculin Testing Protocol

A complete medical history was taken from all patients with special attention to risk factors for liver toxicity: alcohol abuse (>40 g/day), use of hepatotoxic drugs, pregnancy or recent childbirth, and a known history of liver disease. A complete physical examination was performed and a tuberculin skin test carried out. A chest x-ray and a sputum

smear for acid-fast bacilli staining (if necessary) were taken. Blood tests included complete blood count, coagulation study, and biochemistry, including glucose, urea, creatinine, sodium, potassium, aspartate aminotransferase (AST), alanine aminotransferase, lactate dehydrogenase, gamma glutamyl transpeptidase, total bilirubin, direct bilirubin, and alkaline phosphatase. Tuberculosis disease was ruled out in all cases. The results of the Mantoux tuberculin skin test were read 72 hours after injection of 2 units of purified protein derivative RT-23. Indurations were considered negative if less than 5 mm in diameter and positive if greater than or equal to 5 mm. To rule out a booster effect in individuals over 55 years old with a negative response, a second tuberculin test was performed 7 to 10 days later and the result of the second test was considered definitive.

### Chemoprophylaxis

Primary prophylaxis was defined as therapy administered to persons at risk in order to prevent tuberculosis infection (before the patient had a positive skin test). Secondary prophylaxis was defined as therapy administered against latent tuberculosis infection (in a patient with a positive tuberculin test). Prophylaxis was prescribed according to the current recommendations of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR).<sup>11</sup> All subjects who had negative tuberculin tests and were aged 20 years or younger were prescribed primary prophylaxis. Primary prophylaxis was also prescribed for a few individuals who were at special risk, regardless of age. Treatment of latent infection was prescribed for individuals with positive tuberculin tests who had never before been treated. The tuberculin test was repeated after 2 months in contacts older than 20 years of age whose first tests were negative to determine if conversion had taken place. The same criteria for prescribing prophylaxis were then applied.

Primary prophylactic treatment consisted of a daily self-administered dose of 300 mg of isoniazid and 50 mg of vitamin B<sub>6</sub> for 2 months. Secondary prophylaxis consisted of the same treatment applied for 6 months. All subjects were informed of the objectives of the study and signed consent forms before being enrolled. Before treatment was initiated, the main signs and symptoms of hepatotoxicity were explained and subjects were recommended to call the respiratory medicine clinic upon the appearance of any such sign or symptom and to suspend treatment should jaundice, choloria, or deterioration of general health with fever or abdominal pain develop. Patients were informed of the need to abstain from alcohol intake during treatment and to avoid taking hepatotoxic drugs.

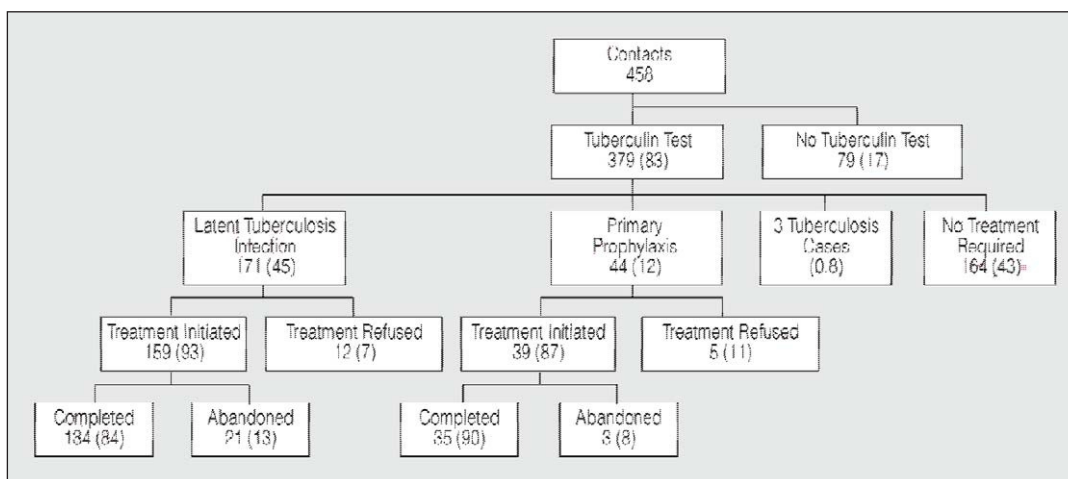
### Evaluation of Adherence to Treatment and Side Effects

While treatment lasted, patients were checked at 15, 30, 60, 120, and 180 days by way of a clinical interview with the physician and a blood test for the parameters described previously.

A patient was considered adherent to treatment if he or she attended scheduled check ups so that analyses could be performed. Patients were considered to have abandoned treatment for no apparent reason if they failed to come to a scheduled clinical appointment.

Patients were asked explicitly about signs and symptoms of liver toxicity such as jaundice, choloria, abdominal pain,

**Figure 1. The 79 tuberculosis cases found, distributed according to tuberculin test results and treatment. The values shown are absolute numbers with percentages between parentheses.**



and unexplained fever whether accompanied by nausea and vomiting or not. Liver toxicity was assessed following the categories of the World Health Organization: grade 1 if the AST level was between 51 and 125 U/L or 1.25 to 2.5 times the normal level; grade 2 if AST was between 126 and 250 U/L or 2.6 to 5 times the normal level; grade 3 if AST was between 251 and 500 U/L or 5.1 to 10 times the normal level; grade 4 if AST was 500 U/L or more or over 10 times the normal level, or if symptoms occurred in a context of AST levels exceeding 250 U/L.<sup>12</sup> Grades 1 and 2 indicated mild liver toxicity and grades 3 and 4 indicated severe toxicity. Viral hepatitis was ruled out by serology in all patients with elevated liver enzymes during treatment. Treatment was interrupted for individuals with grade 3 or 4 toxicity and their liver enzyme levels were monitored weekly. Treatment was restarted when levels became normal and suspended if toxicity reappeared. If the patient refused to restart isoniazid treatment, alternative therapy with 600 mg of rifampicin per day for 4 months was offered.

Side effects unrelated to liver toxicity, such as pruritus, erythema, asthenia, headache, muscle pains, tingling, nausea, vomiting, diarrhea, or constipation were recorded prospectively, along with any other sign or symptom considered to be treatment related. Unexplained variations in analytical findings were also considered side effects. Adverse effects were classified as serious when they required specific health care or suspension of treatment and mild in all other cases.

### Statistical Analysis

Normally distributed values were expressed as means (SD). The frequency in the population of each risk factor (age, sex, alcohol abuse, treatment, pregnancy, peripartum, hepatotoxic drug intake, and previous liver disease) and each dependent variable (hepatotoxicity and adherence to treatment) was calculated. The association of each risk factor and each dependent variable was calculated using a  $\chi^2$  test or a Fisher exact test when required, along with estimation of the odds ratio and 95% confidence intervals. A multiple logistic regression analysis was performed to determine independent risk factors when indicated. Statistical significance was set at a *P*-value less than .05. Data was analyzed using the RSigma 2.0 and Epi-Info 6.1 programs.<sup>13</sup>

## Results

### Participants

Between December 1996 and December 2002 we identified 458 contacts of 79 HIV negative patients with pulmonary tuberculosis confirmed by acid-fast bacilli stain or culture. That number corresponded to completion of conventional contact investigations for 64% of the patients diagnosed with tuberculosis in our public health care area and all pulmonary tuberculosis cases with bacteriological confirmation in HIV negative individuals. Figure 1 shows how the study evolved. Tuberculin testing was completed in 379 contacts (83%), with an average of 4.7 contacts per index case (range, 1-9). Three new cases of tuberculosis disease (prevalence 0.8%) were found. All were living in the index patient's home. Contacts of those cases were likewise studied and enrolled. Latent tuberculosis infection was found in 171 contacts (45%). Treatment was prescribed for 215 individuals (57%), 198 of whom (92%) initiated treatment and were enrolled. The characteristics of treated individuals are summarized in Table 1.

The mean age of individuals accepting treatment—87 men (44%) and 111 women—was 34 years (range, 10-79). Risk factors identified were age 35 years or older (97 of the treated contacts [49%] enrolled), immigrant status (21 [10.6%]), alcohol intake (10 [5%]), and known history of liver disease (3 [1.5%]). No women who were pregnant or who had recently given birth were enrolled; nor were any taking potentially hepatotoxic drugs. None was an intravenous drug user or HIV positive.

### Adherence to Prophylaxis and Course of Treatment

Seventeen (8%) of the 215 contacts who were prescribed prophylaxis refused treatment at the start; 5 (29%) of them were immigrants. One hundred ninety-eight started treatment, 39 (20%) receiving primary

TABLE 1  
Characteristics of the 198 Contacts of Tuberculosis Patients Who Initiated Preventive Treatment

Variable	No. of Patients (%)
Age, years	
10-19	41 (20.7)
20-34	60 (30.3)
35-49	68 (34.3)
50-64	21 (10.6)
>64	8 (4.1)
Sex	
Men	87 (44)
Women	111 (56)
Alcohol abuse, >40 g/day	
No	188 (95)
Yes	10 (5)
History of liver disease	
No	195 (98.5)
Yes	3 (1.5)
Intravenous drug addiction	
No	100 (100)
Yes	0 (0)
Country of origin	
Spain	177 (89.4)
Ecuador	12 (6.1)
Peru	5 (2.5)
Morocco	1 (0.5)
United Kingdom	2 (1)
Italy	1 (0.5)

prophylaxis and 159 (80%) receiving secondary prophylaxis. One hundred sixty-nine individuals (79%) completed the chemoprophylactic protocol. By prophylactic treatment type, 35 were primary (80% of whom were completers) and 135 were secondary (79% of whom were completers).

Twenty-four (12%) abandoned treatment. The reason for withdrawal was unknown in 20 individuals (2 of whom were drinkers of alcohol). For 3, the reason was mild liver toxicity and for a single patient the reason was persistent epigastric pain. The breakdown of patients who did not come to scheduled check ups is as follows: 1 at 15 days, 7 at 30 days, 6 at 60 days, and 10 at 120 days.

We analyzed factors potentially associated with lack of adherence to the monitoring program, among them age, sex, alcohol abuse, history of prior liver toxicity, or immigrant status (Table 2). Only immigrant status tended to be significantly related to lack of adherence (odds ratio, 3.42; 95% confidence interval, 1.03-11.04;  $P=.02$ ).

#### Assessment of Liver Toxicity and Other Adverse Effects

Forty-three of the treated contacts (22%) developed liver toxicity, which was mild in 40 (93%) and serious in 3 (7%). In most cases, toxicity was asymptomatic, and only 27% developed mild gastrointestinal symptoms. Only 1 of the 3 patients with serious toxicity presented symptoms, which consisted of vomiting and abdominal pain. Physical examination detected no abnormalities and we found no differences in severity of toxicity in relation to the presence or absence of symptoms (Figure 2).

The onset of liver toxicity was distributed throughout treatment. The numbers of persons with hepatotoxicity detected at each check up were 14 cases (33%) at 15 days, 15 (35%) at 30 days, 16 (37%) at 60 days, 23 (53%) at 120 days, and 19 (44%) at 180 days.

The cases of serious toxicity that required interruption of treatment occurred in the second (2 cases) and fourth

TABLE 2  
Degree of Adherence to Prescribed Treatment and Factors Related to Nonadherence\*

Risk Factor	Nonadherers/Total (%)	Adherers/Total (%)	OR (95% CI)	P
Age, years				.10
<35	16/24 (67)	83/169 (49)	1	
≥35	8/24 (33)	86/169 (51)	0.48 (0.18-1.28)	
Sex				.49
Men	9/24 (38)	76/169 (45)	1	
Women	15/24 (62)	93/169 (55)	1.36 (0.52-3.59)	
Alcohol abuse				1
No	23/24 (96)	163/169 (96)	1	
Yes	1/24 (4)	3/169 (4)	1.18 (0.02-10.43)	
History of liver disease				1
No	24/24 (100)	166/169 (98)	1	
Yes	0/24 (0)	3/169 (2)	Not calculable	
Treatment				.42
Primary prophylaxis	3/24 (12)	35/169 (21)	1	
Secondary prophylaxis	21/24 (88)	134/169 (79)	1.83 (0.48-8.19)	
Hepatotoxicity				.33
No	21/24 (88)	129/169 (76)	1	
Yes	3/24 (12)	40/169 (24)	0.46 (0.10-1.75)	
Immigrant				.02
No	18/24 (75)	154/169 (11)	1	
Yes	6/24 (25)	15/169 (89)	3.42 (1.03-11.04)	

\*OR indicates odds ratio; CI, confidence interval.

TABLE 3  
Risk Factors Related to Development of Liver Toxicity\*

Risk Factor	Liver Toxicity		OR (95% CI)	P
	Yes/Total (%)	No/Total (%)		
Age, years				.31
<35	19/43 (44)	82/155 (53)	1	
≥35	24/43 (56)	73/155 (47)	1.42 (0.68-2.96)	
Sex				.07
Men	24/43 (56)	63/155 (41)	1	
Women	19/43 (44)	92/155 (59)	0.54 (0.26-1.13)	
Alcohol abuse				.04
No	38/43 (88)	150/155 (97)	1	
Yes	5/43 (12)	5/155 (3)	3.95 (0.93-16.79)	
Hepatotoxicity				1
No	43/43 (100)	152/155 (98)	1	
Yes	0/43 (0)	3/155 (2)	Not calculable	
Treatment				.03
Primary prophylaxis	3/43 (7)	36/155 (23)	1	
Secondary prophylaxis	40/43 (93)	119/155 (77)	4.03 (1.11-17.40)	
Immigrant				1
No	39/43 (91)	138/155 (89)	1	
Yes	4/43 (9)	17/155 (11)	0.83 (0.22-2.85)	

\*OR indicates odds ratio; CI, confidence interval.

(1 case) months. Two patients re-started prophylaxis with isoniazid. One of them completed treatment and the other suffered a recurrence of liver toxicity, after which treatment was discontinued. The third patient refused to continue taking isoniazid and was switched to rifampicin. Four months of rifampicin treatment were completed without adverse events.

Table 3 presents the univariate analysis of risk factors for liver toxicity. Only type of treatment was independently associated with hepatotoxicity, as shown in Table 4.

A total of 14 treated contacts (7%) suffered side effects that were unrelated to liver toxicity. The types and frequencies of adverse effects were as follows: dyspepsia, 9 cases (64%); allergic reaction with skin rash, 2 cases (14%); asthenia, 2 cases (14%), and gynecomasty, 1 case (7%). We detected no differences in the rates of adverse effects in relation to age (younger or older than 35 years old), sex, or type of treatment. One individual experiencing side effects abandoned treatment and withdrew, 3 had treatment interrupted (1 because of allergy and 2 because of gastrointestinal problems), and 3 were started on rifampicin (1 because of allergy and 2 due to intolerance).

## Discussion

With this prevention program we managed to complete conventional contact investigations in 64% of all tuberculosis cases diagnosed in our public health care area and in all cases of pulmonary tuberculosis with bacteriological confirmation in HIV negative patients. However, scarcity of resources at the time of the study made it impossible to include contacts of the remaining tuberculosis patients, among them those with HIV-related disease (accounting for 18% of all

TABLE 4  
Independent Variables Related to Liver Toxicity\*

Variable	OR	95% CI	P
Sex	0.5561	0.2764-1.1188	.09
Alcohol	1.6596	0.8649-3.1845	.12
Treatment	3.7970	1.0980-13.1300	.03

\*OR indicates odds ratio; CI, confidence interval.

tuberculosis patients diagnosed in our area) who at present must be studied by the diagnosing physicians.

Tuberculin testing was completed in 83% of the contacts identified, and 79% of the contacts who were prescribed prophylaxis completed the regimen. The overall adherence rate was similar to the goals proposed by the public health care plan for the Autonomous Community of Valencia for 2001 to 2004<sup>14</sup> and exceeded the objectives set out in the SEPAR guidelines of 2002.<sup>15</sup> We attribute the program's success to the fact

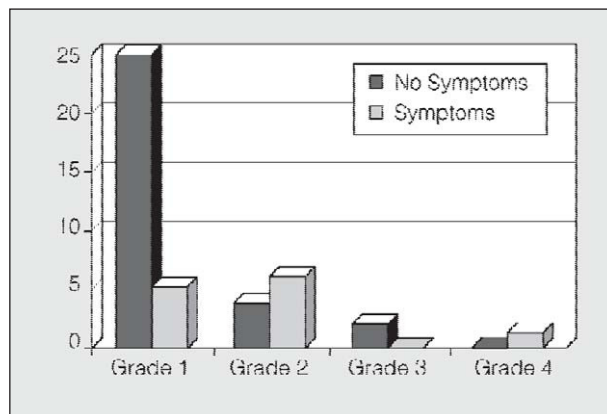


Figure 2. Symptoms of the 43 patients with hepatotoxicity.

that supervision was facilitated by strict monitoring from a specifically-dedicated clinic.

Among the factors potentially related to adherence, only immigrant status (with a 25% rate of withdrawal from treatment) had a significant effect in the population sample we studied. This leads us to the conclusion that different treatment approaches, such as directly observed treatment or short-course therapy,<sup>11</sup> as applied in other groups with traditionally high rates of noncompliance, such as intravenous drug users, alcoholics, indigents, and HIV infected individuals, should also be applied in immigrants, who are of great importance in the control of tuberculosis.

The rate of isoniazid-related liver toxicity, understood as elevated transaminase levels whether accompanied by symptoms or not, was 22%. Only 1.5% of all contacts treated developed serious toxicity, which was kept under control with the usual measures and which did not lead to hospitalization or life-threatening events in any case.

Conventional contact tracing is one of the most effective tuberculosis control measures, following early diagnosis of the disease and the supervision and monitoring of patients during treatment.<sup>1</sup> Valencia and nearly all the autonomous communities in Spain have tuberculosis monitoring programs in effect and most include contact studies.<sup>4,16</sup> Nevertheless, the scarcity of official information on this procedure is noteworthy. Thus, while some authors have reported high percentages (74%-84%) of tuberculosis patients for whom they have been able to trace contacts,<sup>17,18</sup> those findings are inconsistent with information provided by such official organisms as the Center for Prevention and Control of Tuberculosis of the Community of Valencia,<sup>19</sup> whose figures are considerably lower (60% in 1998 and 27.9% in 2002).

We were able to test 83% of the contacts traced. A mean 4.7 contacts per index case were located, a rate similar to those published in the 2 studies that are most representative of the situation in Spain.<sup>3,20</sup> We found 3 new cases of tuberculosis, corresponding to a rate of 0.8%, which is lower than the previously reported ones of 1.8% and 1.3%.<sup>18,20,21</sup> All 3 new cases lived in the index patient's home. Forty-five percent of the contacts given tuberculin tests had latent infections, and that rate was similar to others reported for Spain.<sup>3,20</sup> The finding of new cases, in the first instance, and the provision of adequate treatment of infected contacts as a measure of control, in the second, are the reasons why it is important to carry out conventional contact investigations.<sup>1,11</sup>

The program's most important objective was to improve the rates of adherence to treatment. In this sense the adherence rate observed was fairly high and comparable to rates found in studies evaluating short-course treatment protocols.<sup>22</sup> That finding supports the use of the traditional prophylaxis regimen whose efficacy has been firmly demonstrated in over 50 years of application.

The 22% rate (43 cases) of liver toxicity we found seems high, but is similar to rates found in other studies

that used similar monitoring protocols<sup>22-24</sup>; in those studies the rates of toxicity ranged from 23% to 7%. Such findings confirm that transient transaminase elevations that are predominantly asymptomatic (72% in our study) are common during treatment. It is noteworthy that we saw no correlation between the presence of symptoms and the seriousness of toxicity in our study; thus 2 cases of grade 3 toxicity, in which treatment had to be interrupted, involved no symptoms. This means that those cases would not have been detected if only symptoms had been monitored, and that there would have been a consequent risk of delayed interruption of treatment.<sup>25</sup> We therefore feel that monitoring transaminase levels during treatment provides an additional safety measure, as shown by Byrd et al,<sup>23</sup> Bailey et al,<sup>26</sup> and Stuart et al.<sup>24</sup> Very low rates of toxicity (0.1%-0.3%) and no mortality have been reported by other authors, such as Nolan et al<sup>27</sup> and LoBue and Moser,<sup>28</sup> who have used only clinical monitoring protocols. Such low rates of toxicity may be attributable to the low percentages—ranging from 15% to 20%—of patients over 35 years of age in those studies, given that that toxicity rates increase with age<sup>7,23,26</sup> and for that reason prophylaxis has been advised against in older adults.<sup>29</sup> Only 3 treated individuals (1.5% of all contacts treated) developed serious toxicity, a rate that is lower than those reported by other authors.<sup>22,24</sup> Toxicity appeared at various moments throughout our study and was sometimes at its most intense toward the end—such that we recorded high incidence rates at 4 and 6 months—a pattern also described by other authors.<sup>25,26</sup> The only risk factor we found to be independently related to toxicity was duration of treatment. No correlations were observed between hepatotoxicity and any of the other factors usually reported, such as alcohol,<sup>7</sup> age,<sup>6,7,23,26</sup> or a history of liver disease,<sup>6</sup> although this might be attributable to the small sample size.

In conclusion, our findings support the need to improve control programs to extend the use of contact tracing after patients are diagnosed with tuberculosis and to monitor treatment adequately. We believe that support from the public health authorities is indispensable, as is the centralization of tasks at specialized clinics. Monitoring treatment using both clinical check ups and regular blood tests contributes to adherence and minimizes the frequent problems of toxicity or other side effects of isoniazid, regardless of patient characteristics. Certain groups, such as immigrants, are of great importance in controlling the disease, and they may need special short-duration treatment protocols or directly-observed treatment to improve adherence.

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