Clinical Characteristics and Treatment Outcomes of Patients with Isoniazid-Monoresistant Tuberculosis

Adithya Cattamanchi,[1] Raymund B. Dantes,[2] John Z. Metcalfe,[1] Leah G. Jarlsberg,[1] Jennifer Grinsdale,[4] L. Masae Kawamura,[4] Dennis Osmond,[3] Philip C. Hopewell,[1] and Payam Nahid[1]

[1]Division of Pulmonary and Critical Care Medicine and Departments of [2]Medicine and [3]Epidemiology and Biostatistics, University of California, San Francisco, and [3]Tuberculosis Control Section, San Francisco Department of Public Health, San Francisco, California

Background. Risk factors and treatment outcomes under program conditions for isoniazid (INH)–monoresistant tuberculosis have not been well described.

Methods. Medical charts were retrospectively reviewed for all cases of culture-confirmed INH-monoresistant tuberculosis ($n = 137$) reported to the San Francisco Department of Public Health Tuberculosis Control Section from October 1992 through October 2005, and those cases were compared with a time-matched sample of drug-susceptible tuberculosis cases ($n = 274$).

Results. In multivariate analysis, only a history of treatment for latent tuberculosis (odds ratio [OR], 3.1; 95% confidenc interval [CI], 1.5–6.4; $P = .003$) or for active tuberculosis (OR, 2.7; 95% CI, 1.4–5.0; $P = .002$) were significantl associated with INH-monoresistant tuberculosis. Of the 119 patients who completed treatment, 49 (41%) completed a 6-month treatment regimen. Treatment was extended to 7–12 months for 53 (45%) of the patients and to >12 months for 17 (14%). Treatment was most commonly extended because pyrazinamide was not given for the recommended 6-month duration (35 patients [29%]). Despite variation in treatment regimens, the combined end point of treatment failure or relapse was uncommon among patients with INH-monoresistant tuberculosis and was not significantl different for patients with drug-susceptible tuberculosis (1.7% vs. 2.2%; $P = .73$).

Conclusions. A history of treatment for latent or active tuberculosis was associated with subsequent INH monoresistance. Treatment outcomes for patients with INH-monoresistant tuberculosis were excellent and were no different from those for patients with drug-susceptible tuberculosis. However, new, short-course regimens are needed because a small proportion of patients completed the 6-month treatment regimen recommended by the American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Diseases Society of America, primarily because of pyrazinamide intolerance.

Despite >50 years of availability of antituberculosis chemotherapy, tuberculosis remains a leading infectious cause of death worldwide, with 9 million new cases and nearly 2 million deaths annually [1]. Compounding the challenges of an already lengthy and complicated treatment course, the World Health Organization reported in 2008 the highest number of cases of drug-resistant tuberculosis to date. Isoniazid (INH) is an important first-lin agent for treatment of tuberculosis, because of its potent early bactericidal activity. However, resistance to INH, alone or in combination with other drugs, is now the second most common type of resistance worldwide, with current prevalence estimated at 10.3% for new cases and 27.7% for previously treated cases (13.3% combined) [2].

Given the increasing global numbers of INH-resistant tuberculosis cases, the effect of such resistance on treatment outcomes is of particular interest. A review published in 1986 of 12 British Medical Research Council clinical trials from sub-Saharan Africa, Hong Kong, and Singapore in the 1970s and 1980s reported a low rate of treatment failure (2%) for INH-resistant strains treated with an initial 4–5-drug regimen containing rifampin for at least 6 months [3]. Largely on the basis of this review, the American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC), and Infectious Diseases Society of America (IDSA) issued a

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Reprints or correspondence: Dr. Adithya Cattamanchi, San Francisco General Hospital, Rm. 5K1, Pulmonary Div., 1001 Potrero Ave., San Francisco, CA 94110 (acattamanchi@medsfgh.ucsf.edu).

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guideline recommending treatment with a standard 4-drug regimen (INH, rifampin, pyrazinamide, and ethambutol) for 6 months, with discontinuation of INH after the results of drug-susceptibility tests are known [4]. However, contemporary studies are still needed to better characterize risk factors for INH-monoresistant tuberculosis, as well as to evaluate the efficac of current treatment guidelines under program conditions.

To address these issues, we conducted a retrospective evaluation of tuberculosis cases reported to the San Francisco Department of Public Health (SFDPH) Tuberculosis Control Section. Our objectives were to determine risk factors for INH-monoresistant tuberculosis, to identify and describe the variations in treatment regimens for patients with INH-monoresistant tuberculosis, and to compare treatment outcomes for patients with INH-monoresistant tuberculosis with those for patients with drug-susceptible tuberculosis treated under program conditions.

METHODS

Study population and setting. The records of the SFDPH Tuberculosis Control Section were reviewed to identify all cases of culture-confi med, INH-monoresistant tuberculosis reported in San Francisco, California, from 1 October 1992 through 31 October 2005. Cases were excluded if INH resistance was acquired during treatment or if resistance to any other first-lin antituberculosis medication was documented. For each INH-monoresistant tuberculosis case identified the next 2 reported cases of drug-susceptible tuberculosis were selected to establish a time-matched comparison cohort. Drug-susceptible tuberculosis cases were required to have documented susceptibility to INH, rifampin, pyrazinamide, and ethambutol.

Study design. For both drug-susceptible and INH-monoresistant tuberculosis cases, demographic and clinical characteristics were extracted from the SFDPH Tuberculosis Control Section electronic database. In addition, medical charts were retrospectively reviewed using a standardized data-abstraction form to obtain detailed information on prior tuberculosis treatment, treatment regimens, adverse drug reactions, adherence to therapy, and clinical follow-up for 1 year after treatment completion. The study protocol was approved by the University of California, San Francisco, Committee on Human Research.

Definitions Drug susceptibility was confi med in all cases at the SFDPH laboratory by use of the agar-proportion method [5]. INH resistance was classifie as either low level or high level when there was >1% growth of *Mycobacterium tuberculosis* complex in the presence of 0.2 μg/mL or 1 μg/mL of INH, respectively. Treatment was considered completed if all antituberculosis chemotherapy had been administered and there was either microbiological confi mation of cure or an indication in the medical record that the patient had received an effective course of treatment. An adverse drug reaction was define as any symptom or laboratory abnormality leading to interruption of ⩾1 antituberculosis medication. Patients were considered to have nonadherence to treatment if any of the following conditions were met: (1) >14 consecutive days of treatment were missed, (2) >2 consecutive visits to the clinic were missed, or (3) >20% of doses were missed in any month by a patient receiving directly observed therapy. The primary outcomes for the study were (1) a combined end point of treatment failure or relapse and (2) all-cause mortality while receiving tuberculosis treatment. In accordance with ATS/CDC/IDSA guidelines, a patient was considered to have treatment failure if culture results remained positive after 4 months of treatment and to have had a relapse when a second episode of tuberculosis was diagnosed within 1 year after treatment completion [4]. *IS6110* genotyping results were used to confir that the second episodes were true relapses rather than subsequent infections with new *M. tuberculosis* strains, as described elsewhere [6].

Statistical analysis. Statistical analyses were performed using Stata, version 9.0 (Stata Corp.), with the level of signif cance specifie in reference to a 2-tailed, type I error (P value) of <.05. Bivariate analyses were performed using the χ^2 test for dichotomous variables and the Mann-Whitney rank-sum test for continuous variables. A logistic regression model was used to evaluate demographic predictors significantl associated with INH-resistance status. Predictors were included in the model if they were associated with INH resistance at the prespecif ed significanc level of $P < .2$ in bivariate analyses. A Cox proportional-hazards model was constructed to determine the association between the primary predictor (drug-resistance

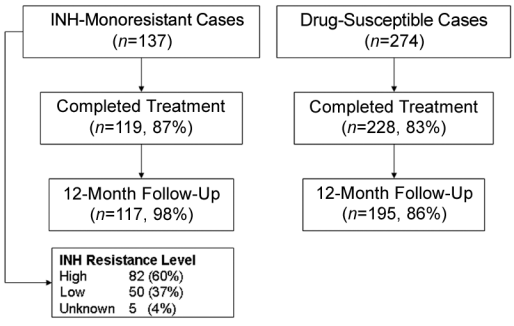

Figure 1. Diagram of the study population. From 1992 through 2005, 137 cases of isoniazid (INH)–monoresistant tuberculosis were reported to the San Francisco Department of Public Health (SFDPH) Tuberculosis Control Section, for which 274 control subjects with drug-susceptible tuberculosis were selected as time-matched controls. The percentage of patients who completed treatment at the SFDPH Tuberculosis Control Section clinic was similar for both groups (87% vs. 83%; $P = .17$), but 12-month follow-up after treatment was completed by a greater percentage of patients with INH-monoresistant tuberculosis, compared with patients with drug-susceptible tuberculosis (98% vs. 86%; $P = .03$).

Table 1. Demographic and clinical characteristics of patients.

Characteristic	Patients with INH-resistant tuberculosis ($n = 137$)	Patients with drug-susceptible tuberculosis ($n = 274$)	P
Male	63	70	.12
Age, median years	47	50	.09
Ethnicity			
Non-Hispanic white	8	11	.30
Non-Hispanic black	4	13	.01
Hispanic	9	14	.17
Asian/Pacific Islander	77	60	<.001
Native American	0.7	1.5	.52
Foreign born	85	72	.002
Homeless or SRO resident	8	19	.004
History of drug or alcohol abuse	13	20	.08
HIV infection	7	15	.01
Prior tuberculosis treatment	36	17	<.001
For active tuberculosis	21	9	<.001
For latent tuberculosis	16	8	.01
Pulmonary tuberculosis	88	88	1.00
Positive AFB smear test	47	41	.29
Cavitary chest radiograph	18	14	.26
Tuberculosis diagnosed in hospital	21	29	.10
Directly observed therapy	52	54	.69
Adherent to treatment	84	84	.96
Adverse reaction	31	15	<.001
Sputum culture conversion at ≤2 months	92	91	.70
Treatment duration, median days	306	220	<.001
Treatment at SFDPH Tuberculosis Control Section clinic	82	65	<.001

NOTE. Data are % of patients, unless indicated otherwise. AFB, acid-fast bacilli; INH, isoniazid; SFDPH, San Francisco Department of Public Health; SRO, single-room-occupancy hotel.

status) and outcome variables. Additional predictor variables were included in the model if either of the following criteria were met: (1) the predictor was associated with the outcome at the prespecifie significanc level of $P < .05$, or (2) the predictor was associated with both the primary predictor and outcome variables at the prespecifie significanc level of $P < .2$. Cox proportional-hazards assumptions were tested using the method of Schoenfeld residuals, and the primary predictor (INH-resistance status) was determined to meet assumptions ($P > .05$). The *c* statistic was calculated as a standard summary measure of model performance.

RESULTS

Study population. During the study period, there were 137 cases of INH-monoresistant tuberculosis reported to the SFDPH Tuberculosis Control Section, for which 274 control subjects with drug-susceptible tuberculosis were selected as time-matched controls. Of the 137 patients with INH-monoresistant tuberculosis, 82 (60%) had high-level INH resistance. The percentage of patients who completed treatment at the SFDPH Tuberculosis Control Section clinic was similar for the group with drug-susceptible tuberculosis and the group with INH-monoresistant tuberculosis (87% vs. 83%; $P = .17$) (figure 1). However, 1-year posttreatment follow-up was completed by a greater percentage of the group with INH-monoresistant tuberculosis (98% vs. 86%; $P = .03$).

Demographic and clinical characteristics. In bivariate

Table 2. Multivariate analysis of demographic characteristics associated with isoniazid resistance.

Characteristic	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P
Ethnicity			
Non-Hispanic black	0.3 (0.1–0.7)	0.5 (0.2–1.6)	.23
Hispanic	0.6 (0.3–1.2)	1.0 (0.3–3.1)	.96
Asian/Pacific Islander	2.3 (1.4–3.7)	1.6 (0.5–4.6)	.40
Foreign born	2.3 (1.3–2.9)	1.0 (0.4–2.4)	.92
Homeless or SRO resident	0.4 (0.2–0.7)	0.6 (0.2–1.5)	.27
Drug or alcohol abuse	0.6 (0.3–1.1)	1.3 (0.6–3.0)	.48
HIV infection	0.4 (0.2–0.8)	0.5 (0.2–1.2)	.11
Prior tuberculosis treatment			
For active tuberculosis	2.8 (1.6–5.0)	2.7 (1.4–5.0)	.002
For latent tuberculosis	2.2 (1.2–4.1)	3.1 (1.5–6.4)	.003

NOTE. SRO, single-room-occupancy hotel.

Table 3. Treatment regimens for isoniazid-monoresistant tuberculosis.

Total duration of treatment, drug regimen (months)	No. (%) of patients (n = 119)
6 Months	49 (41)
HREZ (2), REZ (4)	43 (36)
Other	6 (5)
7–12 Months	53 (45)
HREZ (2), REZ (5–7)	5 (4)
HREZ (9)	3 (3)
HRE (9–12)	2 (2)
HREZ (2), RE (7–10)	23 (19)
HREZ (2), REZ (7–10)	11 (9)
HREZ (2), HRE (7–10)	4 (3)
Other	5 (4)
>12 Months	17 (14)
HRZE (2), RE (>10)	6 (5)
HRZE (2), RZ (>10)	4 (3)
Other	7 (6)

NOTE. Durations are approximate. E, ethambutol; H, isoniazid; R, rifampin; Z, pyrazinamide.

analysis, patients with INH-monoresistant tuberculosis were more likely to be foreign born (85% vs. 72%; $P = .002$) and to have received prior tuberculosis treatment (36% vs. 17%; $P < .001$), compared with patients with drug-susceptible tuberculosis (table 1). In contrast, other risk factors for tuberculosis were less common among the group with INH-monoresistant tuberculosis than among the group with drug-susceptible tuberculosis, including HIV infection (7% vs. 15%; $P = .01$), homelessness (8% vs. 19%; $P = .004$), and a history of substance abuse (13% vs. 20%; $P = .07$). The majority of patients in both groups were of Asian ethnicity, although there was a higher percentage of Asian persons (77% vs. 60%; $P < .001$) and a lower percentage of non-Hispanic black persons (4% vs. 13%; $P = .006$) in the group with INH-monoresistant tuberculosis, compared with the group with drug-susceptible tuberculosis. Filipino (37%) and Chinese (44%) persons accounted for 81% of Asian persons with INH-monoresistant tuberculosis. In a multivariate analysis, only a history of treatment for latent tuberculosis (OR, 3.1; 95% CI, 1.5–6.4; $P = .003$) or for active tuberculosis (OR, 2.7; 95% CI, 1.4–5.0; $P = .002$) were significantl associated with INH monoresistance (table 2).

The clinical presentation of tuberculosis did not differ significantl between the 2 groups. The percentages of patients with fever, night sweats, weight loss, and hemoptysis were similar (all P values $\geq .2$; data not shown). The same percentage of patients in each group presented with extrapulmonary tuberculosis (12%). Factors associated with the extent of disease, such as positive results of acid-fast bacilli smear test (47% vs. 41%; $P = .29$) and cavitation on initial chest radiograph (18% vs. 14%; $P = .26$), were not significantl different between the group with INH-monoresistant tuberculosis and the group with drug-susceptible tuberculosis. There were, however, some differences in characteristics associated with treatment. Patients with INH-monoresistant tuberculosis received a longer duration of treatment (median, 306 vs. 220 days; $P < .001$), were more likely to experience an adverse drug reaction requiring an interruption in therapy (31% vs. 15%; $P < .001$), and were more likely to complete treatment at the SFDPH Tuberculosis Control Section clinic (82% vs. 65%; $P < .001$). Of note, patients who received treatment at the SFDPH Tuberculosis Control Section clinic overall were less likely to have extrapulmonary tuberculosis (10% vs. 19%; $P = .01$) and to die during tuberculosis treatment (5% vs. 16%; $P < .001$) and were more likely to receive directly observed therapy (59% vs. 37%; $P < .001$), compared with patients whose treatment was managed by non–tuberculosis clinic providers.

Treatment regimens. Detailed treatment information was available for all 119 patients with INH-monoresistant tuberculosis who completed treatment. Overall, treatment was given daily in the continuation phase to 117 patients (98%) and was given twice weekly and 3 times weekly to 1 patient each. At least 6 months of treatment with rifampin were completed by 89% of patients, ethambutol by 87%, and pyrazinamide by 56%. INH was continued for 22 (18%) of the patients even after INH resistance was identified 17 (77%) of these 22 patients were infected with *M. tuberculosis* isolates displaying low-level INH resistance. A 6-month treatment regimen was completed by 49 (41%) of the 119 patients, 43 (88%) of whom received first-lin ATS/CDC/IDSA-recommended treatment (table 3). Treatment was extended beyond 6 months for 70 patients (59%), of whom 53 (45%) completed a 7–12-month

Table 4. Reasons for extension of treatment beyond 6 months.

Reason for treatment extension	No. (%) of patients (n = 70)
Pyrazinamide given for <6 months	
All	35 (50)
Because of physician preference	18 (26)
Because of adverse reaction	16 (23)
Hepatotoxicity	8 (11)
Hyperuricemia/gout	4 (6)
Rash	3 (4)
Severe indigestion	1 (1)
Because of pregnancy	1 (1)
Treatment noncompliance	14 (20)
Extrapulmonary tuberculosis	10 (14)
Other[a]	11 (16)

[a] Other reasons included delayed clinical response to treatment (n = 4), delayed culture conversion (n = 6), and participation in a clinical trial (n = 1).

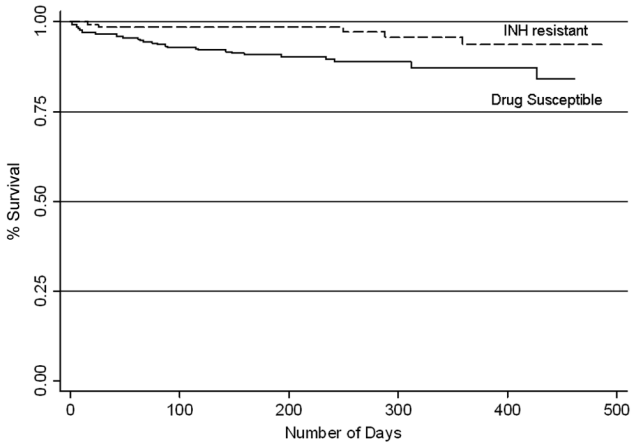

Figure 2. Kaplan-Meier survival curves for patients with isoniazid (INH)–monoresistant tuberculosis *(dashed line)* and drug-susceptible tuberculosis *(solid line).* Survival was significantly greater among patients with INH-monoresistant tuberculosis than among patients with drug-susceptible tuberculosis ($P < .007$, by log-rank test).

course of treatment and 17 (14%) completed a >12-month course. For patients who received extended treatment, 10 different regimens containing first-lin drugs and 18 different regimens containing second-line drugs were used (table 3).

Treatment was extended beyond 6 months for 35 patients (29%) because pyrazinamide was discontinued in the continuation phase of treatment (table 4). For 17 patients (14%), all of whom received treatment before 1997, pyrazinamide was discontinued because of physician preference. Pyrazinamide was discontinued for another 16 patients (13%) during the continuation phase of treatment because of an adverse reaction; of these patients, 8 (7%) had hepatotoxicity. No demographic or clinical characteristics were associated with either pyrazinamide discontinuation or treatment extension beyond 6 months in either bivariate or multivariate analysis (data not shown).

Clinical outcomes. The combined end point of treatment failure or relapse occurred for only 2 (2%) of the patients with INH-monoresistant tuberculosis (both had relapses and both were receiving a daily regimen) and 5 (2%) of the patients with drug-susceptible tuberculosis (2 had relapses and 3 had treatment failures). The treatment regimens used for the 2 patients with INH-monoresistant tuberculosis who had relapses were as follows: INH, rifampin, pyrazinamide, and ethambutol for 2 months followed by rifampin, pyrazinamide, and ethambutol for 4 months for one patient and INH, rifampin, pyrazinamide, and ethambutol for 2 months followed by rifampin and ethambutol for 7–10 months for the other patient. There was no association between INH-resistance status and the combined end point of treatment failure or relapse (OR, 0.75; 95% CI, 0.14–3.92; $P = 0.73$). Multivariate analysis was not performed because of the small number of patients with this end point.

All-cause mortality during tuberculosis treatment was reported for 5 (4%) of the patients with INH-monoresistant tuberculosis and 30 (11%) of the patients with drug-susceptible tuberculosis. Among the group with INH-monoresistant tuberculosis, all-cause mortality was lower for patients with high-level INH resistance than for patients with low-level INH resistance (2% vs. 6%; $P = .30$), although this association was not statistically significant In Kaplan-Meier survival analysis, survival was significantl greater for patients with INH-monoresistant tuberculosis, compared with patients with drug-susceptible tuberculosis ($P < .007$) (figu e 2). Only HIV status, results of sputum acid-fast bacilli smear examination, age, in-hospital diagnosis of tuberculosis, and treatment location satisfie the prespecifie criteria for inclusion in a multivariate analysis of all-cause mortality. After adjustment for these factors, the association between INH monoresistance and decreased all-cause mortality (hazard ratio, 0.43; 95% CI, 0.16–1.13; $P = .09$) (table 5) did not reach the prespecif ed threshold for statistical signif cance.

DISCUSSION

In this study, we performed the largest comparison reported to date of clinical characteristics and treatment outcomes between patients with INH-monoresistant tuberculosis and patients with drug-susceptible tuberculosis under program con-

Table 5. All-cause mortality during treatment for tuberculosis.

Predictor variable	Unadjusted OR (95% CI)	Adjusted HR[a] (95% CI)	*P*
INH monoresistance	0.31 (0.12–0.81)	0.43 (0.16–1.13)	.09
HIV infection	2.82 (1.24–6.45)	2.46 (0.94–6.47)	.07
Positive AFB smear test	3.18 (1.51–6.68)	3.19 (1.50–6.80)	.003
Age >65 years	3.37 (1.67–6.81)	4.02 (1.72–9.04)	.001
Tuberculosis diagnosed in the hospital	3.36 (1.66–6.80)	2.10 (1.06–4.15)	.03
Treatment at SFDPH Tuberculosis Control Section clinic	0.28 (0.14–0.57)	0.40 (0.20–0.83)	.01

NOTE. AFB, acid-fast bacilli; HR, hazard ratio; INH, isoniazid; SFDPH, San Francisco Department of Public Health.
[a] Cox proportional-hazards model (*c* statistic, 0.79).

ditions. We found that a history of treatment for latent or active tuberculosis was strongly associated with subsequent INH monoresistance. With regard to treatment outcomes, we found that both the ATS/CDC/IDSA-recommended 6-month treatment regimen (INH, rifampin, pyrazinamide, and ethambutol for 2 months followed by rifampin, pyrazinamide, and ethambutol for 4 months) and extended treatment regimens for INH-monoresistant tuberculosis were highly effective, resulting in only 2 cases of relapse. However, our finding suggest that new, short-course treatment regimens are needed, because at least 13% of patients were unable to tolerate pyrazinamide during the continuation phase of treatment.

Our multivariate analysis showed that prior tuberculosis treatment was the only risk factor significantl associated with INH monoresistance. Although previous studies have reported an association between prior treatment for active tuberculosis and INH monoresistance [7–11], our analysis demonstrates that INH therapy for latent tuberculosis infection may also increase the risk of INH-resistant tuberculosis. This fi ding is in line with the results of a recent meta-analysis of trials of INH preventive therapy, in which the authors concluded that a significan association between INH preventive therapy and drug-resistant tuberculosis could not be excluded (relative risk, 1.45; 95% CI, 0.85–2.47) [12].

Another findin of concern in our study was the poor tolerability of the first-lin ATS/CDC/IDSA-recommended treatment regimen for INH-monoresistant tuberculosis. This treatment regimen was discontinued for 13% of patients because of an adverse reaction to pyrazinamide, most commonly hepatotoxicity. We had limited statistical power to determine whether treatment with rifampin and pyrazinamide alone in the absence of INH [13], use of pyrazinamide in the continuation phase [14], or other factors were associated with the high proportion of pyrazinamide-related adverse events observed in our study. However, similar finding were reported for a cohort of mostly drug-susceptible tuberculosis cases in Montreal, Quebec, in which the incidence of major adverse reactions was at least 3 times higher with use of pyrazinamide, compared with use of INH, rifampin, and ethambutol [15]. Alternative short-course regimens that do not require extended use of pyrazinamide are clearly needed for treatment of INH-monoresistant tuberculosis.

An unanticipated findin of our study was the decreased all-cause mortality during tuberculosis treatment among patients with INH-monoresistant tuberculosis, compared with that among patients with drug-susceptible tuberculosis. This fi ding should be interpreted with caution, because it failed to meet the prespecifie threshold for statistical significanc in multivariate analysis and because of the limitations inherent in a retrospective analysis. It is possible that the decreased all-cause mortality observed among the cohort with INH-monoresistant tuberculosis may be partly explained by differences between the case and control populations, such as the presence of comorbid medical conditions, the severity and extent of tuberculosis, and variations in clinical care, for which we were unable to adjust in our analyses. Nonetheless, there are biologically plausible explanations for a possible association between INH monoresistance and decreased virulence [16–21]. Population-based studies have shown that *M. tuberculosis* strains harboring certain INH-resistance mutations, including a serine-to-threonine substitution at amino acid position 315 of katG, are less likely to generate secondary cases [22, 23]. Similar studies are needed to establish whether these or other mutations have an impact on *M. tuberculosis* virulence in addition to transmission.

In summary, our study identifie prior treatment for latent tuberculosis and prior treatment for active tuberculosis as independent risk factors for subsequent INH monoresistance. This troubling association with INH preventive therapy is in agreement with a recently published meta-analysis [12] and deserves further evaluation. With regard to tuberculosis treatment outcomes, our study offers additional evidence supporting the use of the daily, first-lin treatment regimen currently endorsed by the ATS/CDC/IDSA guidelines for INH-monoresistant tuberculosis [4]. However, the high incidence of drug toxicity suggests that new, short-course regimens are needed to combat the increasing numbers of INH-resistant tuberculosis cases worldwide. Lastly, the association identifie between INH monoresistance and decreased all-cause mortality is intriguing. The hypothesis that mutations conferring INH resistance may decrease *M. tuberculosis* virulence deserves further study.

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Potential confl cts of interest. All authors: no conf icts.

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