

The Effectiveness of a 9-Month Regimen of Isoniazid Alone versus 3- and 4-Month Regimens of Isoniazid plus Rifampin for Treatment of Latent Tuberculosis Infection in Children: Results of an 11-Year Randomized Study

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Background. A 9-month course of isoniazid monotherapy is currently recommended for the treatment of latent tuberculosis infection (LTBI) and has been shown to be effective in both children and adults. Reduced compliance with this regimen has forced physicians to explore shorter regimens. The aim of this study was to compare 3- and 4-month combination regimens of isoniazid plus rifampin with a 9-month regimen of isoniazid monotherapy for the treatment of LTBI in children.

Methods. This prospective, randomized, controlled study was conducted over an 11-year period (1995–2005). In period 1 (1995–1998), 232 patients received isoniazid therapy for 9 months (group A), and 238 patients received isoniazid and rifampin for 4 months (group B). In period 2 (1999–2002), 236 patients were treated with isoniazid and rifampin for 4 months (group C), and 220 patients received the same regimen for 3 months (group D). All patients were observed for ≥ 3 years.

Results. Overall compliance with treatment was good, but patients who received isoniazid monotherapy were less compliant than were those who received short-course combination therapy ($P = .011$, for group A vs. group B; $P = .510$, for group C vs. group D). No patient in any group developed clinical disease during the follow-up period. New radiographic findings suggestive of possible active disease were more common in patients who received isoniazid monotherapy (24%) than in those treated with shorter regimens (11.8%, 13.6%, and 11% for groups B, C, and D, respectively; $P = .001$ for group A vs. group B; $P = .418$ for group C vs. group D). Serious drug-related adverse effects were not detected.

Conclusions. Short-course treatment with isoniazid and rifampin for 3–4 months is safe and seems to be superior to a 9-month course of isoniazid monotherapy.

Although treatment of patients with active tuberculosis (TB) is the first priority for TB control, the identification and treatment of patients with latent TB infection (LTBI) is also important [1]. Treatment of LTBI

with isoniazid greatly reduces the likelihood that active TB will develop and decreases the number of adults with active disease who will transmit infection to others, as demonstrated by a number of controlled clinical trials [2–5]. Administration of isoniazid chemoprophylaxis for 3, 6, and 12 months reduced the risk of TB by 21%, 65%, and 75%, respectively [6]. More recent data suggested that 9 months of isoniazid chemoprophylaxis may offer optimal protection; this regimen is currently recommended by the American Academy of Pediatrics for children and adolescents [2, 7]

Adherence to treatment regimens has been recognized as a major problem for TB control, especially

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with regard to the treatment of LTBI [2, 6, 8, 9]. Isoniazid chemoprophylaxis is most effective when the compliance rate is high (>80% of doses taken) [6].

The prevalence of isoniazid-resistant TB in individuals who emigrate from certain developing-to-developed countries is high [10, 11]. Administration of rifampin monotherapy for 6 months is recommended for the treatment of LTBI in children who are infected with an isoniazid-resistant but rifampin-susceptible organism [2, 12]. However, to our knowledge, there has only been 1 randomized clinical trial that evaluated rifampin-containing regimens [13]. Ormerod [14] suggested that 3- and 4-month regimens of isoniazid plus rifampin are effective for the treatment of LTBI in children and adolescents. The British Thoracic Society currently recommends 3-month regimens of chemoprophylaxis with isoniazid and rifampin for infants, children, and adolescents who have LTBI [15]. A similar regimen has been successfully applied in certain TB centers in South Africa [16].

We designed a prospective, randomized study that compared isoniazid monotherapy with short-course regimens that contained isoniazid and rifampin to provide support for new strategies for the treatment of LTBI in children and adolescents. Three regimens were used: isoniazid taken daily for 9 months, isoniazid and rifampin taken daily for 4 months, and isoniazid and rifampin taken daily for 3 months. The objectives of the study were (1) to determine and compare patient adherence and treatment completion rates without the use of directly observed therapy; (2) to document potential adverse effects associated with 2-drug combination therapy, compared with monotherapy; and (3) to record the outcomes for patients who received monotherapy, compared with the outcomes for those who received short-course combination regimens.

PATIENTS AND METHODS

Study setting and design. This prospective, randomized, controlled study was conducted over an 11 year-period (1995–2005) at the TB clinic of the Second Department of Pediatrics of Athens University (Athens, Greece). The TB clinic is a referral center for children with *Mycobacterium tuberculosis* infection or disease that serves almost 50% of the Greek pediatric patient population (age, <15 years), which is estimated to be ~900,000 children. The study was approved by the Ethics Committee of the P. and A. Kyriakou Children's Hospital (Athens). Parents of participating children signed an informed consent form during their first clinic visit. They also received a detailed handout in their native language that provided useful information related to TB and to the purpose of the study (the handout can be viewed at <http://www.pedtb.gr>). Each patient had an individual electronic file that included demographic, epidemiologic, and clinical characteristics, as well as comments regarding patient adherence to treatment, drug-related adverse

effects, and changes in radiographic findings during and after the end of chemotherapy.

Patients were enrolled during 2 time periods (period 1, from 1 January 1995 through 31 December 1998; and period 2, from 1 January 1999 through 31 December 2002). Patients were observed until December 2005, when 3 years had passed after the last patient was enrolled. During each study period, patients were randomly assigned to 1 of 2 groups on the basis of their number in the clinic (odd or even). In period 1, patients in group A (control group) received isoniazid for 9 months, and those in group B were treated with isoniazid and rifampin for 4 months. In period 2, patients in group C received isoniazid and rifampin for 4 months, and those in group D received the same treatment for 3 months.

Study population and inclusion criteria. The study population included children aged <15 years whose cases fulfilled the International Union Against Tuberculosis and Lung Disease, American Academy of Pediatrics, and British Thoracic Society criteria for LTBI [2, 6, 15]. All children were asymptomatic and had positive tuberculin skin test (TST) results and normal chest radiograph findings or radiographs that indicated inactive fibrotic or calcified parenchymal and/or lymph node lesions. Infection was considered to be recent if documented exposure occurred ≤ 2 years before evaluation. Infection that occurred >2 years before presentation was characterized as “past” and “unknown,” if the time of infection could not be determined.

Tuberculin LOT 5180A (Pasteur Merieux) with Tween 80, containing 5 IU/0.1 mL of solution, was used for the skin test. The result was measured at 72 h by experienced pediatricians at the TB clinic. Patients aged ≥ 3 years with a TST induration ≥ 10 mm who had contact with an index case and/or who had radiograph findings suggestive of LTBI were considered to have a positive result. For patients aged <3 years who had the same risk factors, a measurement ≥ 8 mm was considered to be a positive result. The TST cutoff value was increased from the recommended 5 mm to 8 mm to avoid including patients with nontuberculous mycobacterial infection and to have a better selection of the cohort [17]. Children aged ≤ 3 years with a TST induration ≥ 10 mm and children aged >3 years who had a TST induration >14 mm as an isolated finding were considered to have positive results, as well [2]. Patients with a history of bacille Calmette-Guérin (BCG) vaccination were excluded from the study. In Greece, children are vaccinated with BCG at the age of 6 years; immunization is not mandatory. The same policy is followed for immigrant children. Patients with known immunodeficiency or some other chronic condition that may influence the result of the TST were also excluded from the study.

Therapy regimens and patient treatment. Children allocated to group A received isoniazid, 10 mg/kg once daily (maximum dose, 300 mg). Patients enrolled in groups B, C, and D

received isoniazid and rifampin, 10 mg/kg per day (maximum dose, 300 mg and 600 mg, respectively). Drugs were given once daily before lunch. All children had an initial chest radiograph obtained at the beginning of the course (posterior-anterior and lateral). Follow-up radiographs were obtained at 4 months for groups A, B, and C; at 3 months for group D; and then 1 and 3 years after the completion of treatment. The duration of follow-up was 7–11 years for patients enrolled in period 1 and 3–7 years for those enrolled in the second study period. After the 3-year visit, follow-up continued with telephone interviews every 2 years.

Blood tests to detect possible liver toxicity were not performed routinely. Instead, parents were given detailed instructions regarding the recognition of symptoms that may suggest drug-related adverse effects [2, 15]. Adherence to treatment was determined using urine strips that detect isoniazid metabolites and the presence of rifampin [18]. The test was performed at home by the parents on the last 2 days of each month of treatment and was posted to the clinic free of charge. Parents were advised to perform the test 3–4 h after administration of medicines and to post it within 24 h. Regular presence of drug metabolites in monthly posted urine strips and clinic attendances were the 2 factors that defined compliance with treat-

ment. Compliance was considered to be excellent if patients sent urine strips that were positive for drugs and followed their appointments without delay. Compliance was defined as moderate if patients had to be reminded with telephone contact by the study nurse to send the urine strips or to return for follow-up visits; patients were included in this group if they finally responded to reminder calls. Compliance was considered to be poor if no medication was detected in >2 urine strips in group A (the 9-month treatment period), and in ≥ 1 urine strip in groups B–D (3–4 month treatment period). Compliance was also considered to be poor if patients did not return for follow-up visits, despite having received reminder phone calls, or if they were lost to follow-up. Patients with poor compliance were not included in the treatment outcome analysis; however, they were included in the compliance analysis.

Chest radiographs were interpreted by a pediatric radiologist and 2 consultant pediatricians experienced in TB, in accordance with current recommendations [19]. Physicians who interpreted the radiographs were blinded to the group allocation, and positive radiography findings were recorded only if there was agreement between at least 2 physicians.

Statistical analysis. The presence of differences in patients' characteristics at enrollment and in the various outcomes be-

Table 1. Demographic characteristics of patients enrolled in the study during 1995–1998 (period 1) and 1999–2002 (period 2).

Characteristic	Period 1			Period 2		
	Group A (n = 232)	Group B (n = 238)	P ^a	Group C (n = 236)	Group D (n = 220)	P ^a
Male sex	120 (51.7)	114 (47.8)	.039	136 (57.6)	106 (48.2)	.043
Age						
Mean years \pm SD	9.1 \pm 3.7	9.2 \pm 3.3		8.4 \pm 3.4	7.9 \pm 3.6	
0–5 years	34 (14.6)	35 (14.7)	.963	50 (21.2)	58 (26.4)	.208
6–10 years	109 (47.0)	109 (45.8)		110 (46.6)	106 (48.2)	
≥ 11 years	89 (38.4)	94 (39.5)		76 (32.2)	56 (25.5)	
Greek nationality	142 (61.2)	149 (62.6)	.751	90 (38.1)	87 (39.5)	.839
Immigrant						
All	90 (38.8)	89 (37.4)	.991	146 (61.8)	133 (60.5)	.902
From Albania	34 (14.6)	42 (17.6)		53 (22.4)	54 (24.5)	
From the former Soviet Union	50 (21.5)	43 (18)		65 (27.5)	57 (25.9)	
Native language of Greek ^b	197 (84.9)	205 (86.1)	.707	119 (50.4)	104 (47.3)	.501
Education level of 9–16 years						
Father	184 (79.3)	198 (83.2)	.281	190 (80.5)	182 (82.7)	.541
Mother	189 (81.5)	188 (79.0)	.501	200 (84.8)	187 (85.0)	.940
Privately owned residence	97 (41.8)	104 (43.7)	.679	125 (53.0)	114 (51.8)	.806
Unemployed father	13 (5.6)	10 (4.2)	.481	11 (4.7)	12 (5.4)	.699
Family size of 3–5 persons	205 (88.4)	204 (85.7)	.393	198 (83.9)	188 (85.5)	.645
Two to 4 bedrooms in residence	215 (92.7)	226 (95.0)	.303	194 (82.2)	185 (84.1)	.591

NOTE. Data are no. (%) of subjects, unless otherwise indicated. Group A received isoniazid therapy for 9 months, groups B and C received isoniazid and rifampin for 4 months, and group D received isoniazid and rifampin for 3 months.

^a Determined by the χ^2 test or Student's *t* test.

^b A large number of the economic immigrants were Greek repatriates from the former Soviet Union and Albania.

tween the treatment regimes (i.e., compliance and radiographic findings) was assessed using the χ^2 test or Student's *t* test, as appropriate. The level of significance was fixed at $\alpha = 5\%$. Statistical analysis was performed using SPSS software, version 11.5 (SPSS).

In the comparison of compliance rates in the short-term treatment regimens (groups C and D), we also tested the hypothesis that group D was not inferior, in terms of compliance (excellent/moderate vs. poor), to group C. For patients with poor compliance, treatment outcomes, such as clinical TB and new radiographic findings, could not be evaluated. We could analyze these patients using an intention-to-treat approach and consider them to have experienced treatment failure. However, because there were very few treatment failures among patients who completed treatment, we used the as-treated approach; therefore, patients with poor compliance were not included in the analysis of treatment outcome.

RESULTS

Patients' characteristics. A total of 926 patients fulfilled the criteria for inclusion in the study. Of them, 470 children were enrolled during period 1, and 456 were enrolled during period 2. There were no significant differences in the demographic characteristics between patients in the 2 different groups during each study period (table 1). Of note is the relatively high parental education level and the families' standards of living. It is also noteworthy that, during period 2, there was an increase in the proportion of immigrant children, a lower proportion of native Greek-speaking families, and an increase in the number of patients who were aged ≤ 5 years ($P < .001$; data not shown in tables). The epidemiological and radiological characteristics were similar between patients in different groups (tables 2 and 3). A higher proportion of patients in groups A

and D had recent infection, compared with those in groups B and C.

Patients' compliance with treatment. Overall, a total of 850 (91.8%) of 926 patients had either excellent or moderate compliance. The rest had poor compliance either with treatment or with follow-up examinations (table 4). Compliance was better in group B than in group A; the difference in compliance between groups C and D was not significant (table 4). Poor compliance was more common for patients initially assigned to group A than for patients in group B ($P = .029$). The rate of poor compliance was not significantly different between groups C and D ($P = .533$). Of the 32 patients with poor compliance in group A, 17 (53%) either did not return for follow-up examinations after the fourth month or received $< 80\%$ of total treatment. The main reasons for moderate compliance are shown in table 4.

Patients' follow-up data. Among the patients with excellent or moderate compliance, new radiographic findings, such as hilar adenopathy and/or parenchymal lesions suggestive of possible active disease, were seen during follow-up examination 4 months after the initiation of treatment in 48 (24%) of 200 patients in group A, compared with 26 (11.8%) of 220 patients in group B ($P = .001$). New radiographic findings were found in 30 (13.6%) of 221 compliant patients in group C and in 23 (11%) of 209 compliant patients in group D ($P = .418$). All of these patients were subsequently treated for active disease and received a total of 9 months of treatment with isoniazid and rifampin.

All children who participated in the study responded well to treatment, and no cases of clinical TB were documented at the end of therapy and during follow-up. Serious drug-related adverse events were not detected in any of the patients participating in the study. Nausea and epigastric pain were reported

Table 2. Epidemiological characteristics of patients enrolled in the study during 1995–1998 (period 1) and 1999–2002 (period 2).

Characteristic	Period 1			Period 2		
	Group A (n = 232)	Group B (n = 238)	<i>P</i> ^a	Group C (n = 236)	Group D (n = 220)	<i>P</i> ^a
Means of patient identification						
Screening	170 (73.3)	180 (75.6)	.558	169 (71.6)	146 (66.3)	.191
Contact investigation	62 (26.7)	58 (24.4)	NS	67 (28.3)	74 (33.6)	NS
Source case identified	96 (41.4)	99 (41.6)	NS	98 (41.5)	87 (39.5)	NS
Intrafamilial infection ^b	70 (30.2)	72 (29.8)	NS	68 (28.8)	66 (30)	NS
Recent infection	149 (64.2)	126 (52.9)	.013	124 (52.5)	148 (67.2)	.016

NOTE. Data are no. (%) of subjects, unless otherwise indicated. Group A received isoniazid therapy for 9 months, groups B and C received isoniazid and rifampin for 4 months, and group D received isoniazid and rifampin for 3 months. NS, not significant

^a Determined by the χ^2 test.

^b The infection was considered to be intrafamilial if there was documented household exposure to an adult index case within the previous 2 years.

by 13 (6.5%) of 200 compliant patients in group A, and a transient increase in liver enzyme levels (≤ 3 times the upper limit of normal) was reported in 12 patients (6%). Of the 650 patients enrolled in the short-term treatment groups, 8 children (1.2%) had a transient increase in liver enzyme levels, 5 (0.7%) reported nausea or epigastric pain, 9 (1.3%) had a transient maculopapular rash, and 5 (0.7%) had a photosensitivity reaction. Discontinuation or modification of treatment was not required in any patient.

DISCUSSION

To our knowledge, this is the first study to prospectively evaluate the effectiveness of short-course preventive therapy regimens for children for the treatment of LTBI. A sufficiently large number of children were enrolled and observed for minimum period of 3 years. The study demonstrated that short-course, 3–4-month courses of combination therapy (isoniazid plus rifampin) are well tolerated and are associated with superior compliance—and at least equal efficacy—to 9-month regimens of isoniazid monotherapy. Similar studies have previously shown the effectiveness and safety of short-course therapy for LTBI in adults [20].

Previous studies have shown that isoniazid prophylaxis is effective for the treatment of LTBI if compliance is high and if the isolate is susceptible to isoniazid [5, 6, 21]. The effectiveness of such a regimen was also proven in our study.

New radiographic findings indicating “possible active disease” were identified in a considerable number of children in all groups 4 months after initiation of treatment. The development of new radiographic findings during TB treatment in children is not uncommon [22]. It is well known that TB in children may be characterized by the development of nonspecific signs and symptoms or by radiographic findings solely, and it is often difficult to distinguish between infection and disease [23–25]. In addition, the interpretation of chest radiographs may be subjective, and there are often subtle findings. On the other hand, apparently normal chest radiograph find-

ings do not rule out pulmonary TB or LTBI in children [24, 26]. An important finding of this study was that children who received isoniazid monotherapy had a higher rate of “radiological” disease. It may be hypothesized that combination treatment with 2 bactericidal drugs produces a more rapid reduction in bacterial load; this may explain why fewer radiographic changes were seen on follow-up [25].

The rate of completion of a 6-month course of isoniazid monotherapy, when self-administered, ranges from 6% to 60%, with rates of 20%–30% in most series [27–30]. In this study, a high number of patients who received isoniazid monotherapy demonstrated excellent compliance (152 [65.5%] of 232); however, this figure was significantly higher for patients assigned to the short-course treatment groups (78%–89.5%). This finding supports the notion that the shorter the duration of treatment, the better the compliance [6]. This has also been demonstrated in other studies of short-course regimens in which the responsibility of drug administration was given to children and parents, as well as in studies involving adults [16, 31].

The high rate of compliance achieved in all treatment groups may be related to the continuous and close communication between the clinic pediatricians and the patient’s family. Other factors that may have positively influenced compliance were the culture, tradition, and family ties; the relatively high parental education level; and individual characteristics [27, 31]. Provision of enough information to the family physician and adherence to the recommendations have also been recognized as international problems [32–34]. In 32 (49.2%) of the 65 patients who received short-course regimens and who did not complete treatment in this study, the family physician suggested discontinuation of treatment resulting from nonfamiliarity with the study protocol.

Among the 850 treatment-compliant patients included in the study, none experienced progression from LTBI to clinical TB. Although the compliance rate was very high, and although this played a critical role in the observed outcome, we have to consider that some patients may have been infected with mon-

Table 3. Patients’ radiological findings during the study.

	Period 1			Period 2		
	Group A (n = 232)	Group B (n = 238)	P ^a	Group C (n = 236)	Group D (n = 220)	P ^a
Fibrosis or calcification						
Lung parenchyma	12 (5.1)	10 (4.2)	NS	8 (3.4)	7 (3.1)	NS
Lymph nodes	63 (27.1)	62 (26)	NS	75 (31.7)	73 (33.1)	NS
Lung parenchyma and lymph nodes	42 (18.1)	55 (23.1)	NS	68 (28.8)	60 (27.2)	NS
Normal	115 (49.5)	111 (46.6)	NS	85 (36)	80 (36.3)	NS

NOTE. Data are no. (%) of subjects, unless otherwise indicated. Period 1 was from 1995 through 1998, and period 2 was from 1999 through 2002. Group A received isoniazid therapy for 9 months, groups B and C received isoniazid and rifampin for 4 months (during periods 1 and 2, respectively), and group D received isoniazid and rifampin for 3 months. NS, not significant.

^a Determined by the χ^2 test.

Table 4. Patients' adherence to treatment.

Adherence to treatment	Period 1			Period 2		
	Group A (n = 232)	Group B (n = 238)	P ^a	Group C (n = 236)	Group D (n = 220)	P ^a
Compliance			.011			.510 ^b
Excellent	152 (65.5)	185 (77.7)		203 (86.0)	197 (89.5)	
Moderate	48 (20.7)	35 (14.7)		18 (7.6)	12 (5.5)	
Poor	32 (13.8)	18 (7.6)	.029	15 (6.4)	11 (5.0)	.533
Reason for moderate compliance						
Refusal to take medication ^c	21 (43.7)	3 (8.5)	.005	5 (27.5)	2 (16.6)	NS
Nausea/epigastric pain	13 (27)	7 (20)	NS	2 (11.2)	2 (16.6)	NS
Discontinuation of treatment by family physician	5 (10.4)	18 (51.5)	.005	9 (50)	5 (41.6)	NS
Poor understanding of instruction	9 (18.8)	7 (20)	NS	2 (11.2)	3 (25)	NS

NOTE. Data are no. (%) of subjects, unless otherwise indicated. Period 1 was from 1995 through 1998, and period 2 was from 1999 through 2002. Group A received isoniazid therapy for 9 months, groups B and C received isoniazid and rifampin for 4 months, and group D received isoniazid and rifampin for 3 months. NS, not significant.

^a Determined by the χ^2 test.

^b Let P equal the percentage of patients with excellent/moderate compliance. Assuming that the maximum clinical difference allowed for treatment D to be considered noninferior to treatment C in terms of excellent/moderate compliance would be 3% (i.e., one-half of the difference in arms A and B), the P value for testing $H_0: P_C - P_D \geq 3\%$ vs. $H_1: P_C - P_D < 3\%$ is 0.022 ($<.025$, which is the 1-sided 5% significance level); therefore, H_0 is rejected, and treatment D can be considered to be noninferior to treatment C in terms of compliance.

^c No. (%) of patients with moderate compliance.

odrug- or multidrug-resistant strains of *M. tuberculosis*. According to data provided by the Greek National Reference Laboratory for Mycobacterial Infections, the rates of resistance to isoniazid and rifampin and of multidrug resistance increased considerably between 1993 and 2002 in association with the increasing number of immigrants moving from eastern European countries and from the former Soviet Union [11, 35].

Because of the pauci-bacillary nature of noncavitary childhood TB, it is rare for children to develop secondary bacterial resistance. Cases of noncavitary TB disease in children represent primary drug resistance, and as such, they reflect the risk of transmitted drug resistance within a particular community [36,37]. Children generally receive high doses of TB drugs per kilogram of body weight, compared with adults, and the high drug concentrations can possibly overcome resistance, as has been shown in experimental studies and clinical studies [38, 39]. Rifampin has been recommended empirically as the agent of choice in cases of isoniazid-resistant *M. tuberculosis* infection; this recommendation is supported by rifampin's pharmacokinetic and pharmacodynamic characteristics [40, 41]. In regions with considerable rates of resistance to isoniazid, the use of short-course combination regimens of rifampin may offer a therapeutic advantage [15, 16]. This is especially true when the results of susceptibility tests are not available for the index case [2, 40]. Another advantage of the combination treatment is that, if a misclassification is made and the patient actually has active TB, he or she has received adequate treatment by the time that the correct diagnosis is made.

As expected, serious drug-related adverse effects were not documented in our patients for any of the treatment regimens

[2, 15, 40]. Although cost-effectiveness was not analyzed in our study, other studies that have involved adult patients have shown that short-course chemotherapy with isoniazid plus rifampin is more cost-effective than isoniazid monotherapy when given for 12 months or even 9 months [42–44].

The study has certain limitations that need to be mentioned. Ideally, patients should have been randomized into 3 arms during the entire study period. The population examined was somewhat different during the second period, mainly as a result of the increasing number of immigrants. However, the observed differences may not have had a positive effect in the outcome of patients treated with short-term regimens. Second, the study was not conducted in a blinded fashion, but conducting the study in such a manner would have greatly increased the complexity and the cost of the study, making it impossible to perform.

In conclusion, a short-course regimen with isoniazid and rifampin for 3 months has efficacy equal to isoniazid and rifampin for 4 months, and both regimens are superior to 9-month courses of isoniazid treatment for children with LTBI. Short-course regimens prevent progression of infection to disease and are effective against subclinical disease, even in patients who are at higher risk, such as children aged <5 years, patients with recent infection, and persons who have a high bacterial load associated with intrafamilial transmission of infection. Compliance is considerably higher with short-course regimens, which may also be more effective against infection with isoniazid-resistant, rifampin-susceptible mycobacteria. Drug-related adverse effects are generally uncommon in children re-

ceiving anti-TB drugs, and short-course therapy proved to be equally safe.

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