Shortening Treatment in Adults with Noncavitary Tuberculosis and 2-Month Culture Conversion

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Rationale: Cavitary disease and delayed culture conversion have been associated with relapse. Combining patient characteristics and measures of bacteriologic response might allow treatment shortening with current drugs in some patients.

Objectives: To assess whether treatment could be shortened from 6 to 4 months in patients with noncavitary tuberculosis whose sputum cultures converted to negative after 2 months.

Methods: This study was a randomized, open-label equivalence trial. HIV-uninfected adults with noncavitary tuberculosis were treated daily with isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by 2 months of isoniazid and rifampin. After 4 months, patients with drug-susceptible TB whose sputum cultures on solid media were negative after 8 weeks of treatment were randomly assigned to continue treatment for 2 more months or to stop treatment. Patients were followed for relapse for 30 months after beginning treatment.

Measurements and Main Results: Enrollment was stopped by the safety monitoring committee after 394 patients were enrolled due to apparent increased risk for relapse in the 4-month arm. A total of 370 patients were eligible for per protocol analysis. Thirteen patients in the 4-month arm relapsed, compared with three subjects in the 6-month arm (7.0 vs. 1.6%; risk difference, 0.054; 95% confidence interval with Hauck-Anderson correction, 0.01–0.10).

Conclusion: Shortening treatment from 6 to 4 months in adults with noncavitary disease and culture conversion after 2 months using current drugs resulted in a greater relapse rate. The combination of noncavitary disease and 2-month culture conversion was insufficient to identify patients with decreased risk for relapse.

Keywords: tuberculosis; antitubercular agents; isoniazid; rifampin

One of the major obstacles in tuberculosis (TB) control is the long duration of treatment. Six months of standard short-course chemotherapy with rifampin-containing regimens is highly effective, but many patients default. Directly observed therapy improves cure rates but requires substantial program resources.

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Noncavitary disease and sputum culture conversion after 2 months of treatment have been associated with favorable treatment outcomes in patients with pulmonary tuberculosis.

What This Study Adds to the Field

Shortening treatment from 6 to 4 months in adults with noncavitary disease and sputum culture conversion after 2 months of treatment resulted in significantly more relapses among those treated for 4 months with current first line drugs. Better biomarkers, optimized dosing, and the introduction of drugs with new mechanisms of action are likely needed to shorten tuberculosis treatment.

Treatment shortening is among the highest priorities for TB control programs worldwide.

Until recently, few new anti-TB drugs have been available. Earlier studies suggested that a shorter duration of treatment may be adequate for some patients, such as smear- and culture-negative adults (1–3). Two- to four-month regimens have been studied, but mainly in smear-negative TB. In smear-negative, culture-positive patients, relapse rates of 32% with 2 months of treatment, 7 to 13% with 3 months of treatment, and 4% with 4 months of treatment have been reported (2, 4).

Analyses of earlier TB treatment studies reported patient characteristics and measures of bacteriological response during treatment associated with long-term cure (5, 6). Such markers might be used to identify patients for whom treatment could be shortened with available first-line drugs. Sputum culture conversion after 2 months of anti-TB treatment is the best studied surrogate marker of nonrelapsing cure in HIV-uninfected patients with tuberculosis. About 77% of patients with smear-positive TB convert their sputum cultures to negative after 2 months of standard anti-TB treatment (7). In a retrospective review of eight trials performed by the British Medical Research Council, the rate at which cultures turned negative after 2 months of treatment correlated closely with relapse rates when different TB treatment regimens were compared (8). These results have been confirmed in other studies (9, 10). The presence of cavitary disease on chest radiograph at the time of diagnosis also is a strong predictor of relapse after treatment (9–14). The proportion of adults with newly diagnosed TB who have cavitary disease ranges from 40 to 87% (15–17). Patients

with cavitary disease have a higher sputum bacillary load than those with noncavitary disease (18, 19). Cavitary disease at diagnosis and having a positive sputum culture after 2 months of treatment were associated with relapse in a recent phase 3 trial comparing rifampin and rifapentine-containing regimens (9).

Building on this experience, we hypothesized that treatment with current drugs might be shortened from 6 to 4 months in patients with noncavitary disease who had a rapid bacteriological response to treatment. To test this hypothesis, we conducted a multicenter, phase 3, randomized, open-label, two-sided equivalence trial in HIV-uninfected adults with sputum acid fast bacillus smear-positive or -negative, noncavitary, drug-susceptible TB who converted their sputum cultures to negative after 2 months of treatment. Subjects were followed for 30 months after beginning anti-TB treatment. Relapse was the primary study endpoint.

METHODS

Adults at sites in Brazil, the Philippines, and Uganda, aged 18 to 60 years, with smear-positive or negative, culture-confirmed, noncavitary pulmonary TB and relatively normal hematologic, renal, and hepatic function were pre-enrolled and treated with 2 months of daily isoniazid (H), rifampin (R), ethambutol, and pyrazinamide followed by 2 months of daily HR. After completion of 112 doses within 18 weeks, patients with drug-susceptible TB and negative 2-month sputum cultures were randomly assigned to stop treatment or to receive an additional 2 months of HR for a total of 162 doses. Blocked randomization (in blocks of six), stratified by site, was done centrally. Treatment was supervised for at least 5 days each week. All drugs were manufactured under Good Manufacturing Practice standards. Doses were adjusted for weight (*see* online supplement). The institutional review boards of each site approved the protocol, and all patients gave informed consent. Full eligibility criteria and methods are provided in the online supplement.

Patients were evaluated monthly during treatment and then every 3 months during the first year and every 6 months during the second year posttreatment. All subjects with symptoms of recurrent TB were examined and had multiple sputum cultures, repeat chest radiograph, and other tests as indicated. Drug susceptibility testing and IS6110 DNA fingerprinting of initial and recurrent *Mycobacterium tuberculosis* isolates were done for all bacteriologically confirmed recurrences.

The primary endpoint was bacteriological or clinical relapse at 30 months after the initiation of treatment. Secondary endpoints included treatment failure and relapse and unfavorable treatment outcome at 1 and 2 years after completion of TB treatment. All recurrences of TB were reviewed independently by two clinicians. A Data Safety Monitoring Board reviewed monthly reports of enrollment and endpoints and met four times during the trial.

Statistical Methods

The study was a two-sided equivalence trial comparing the efficacy of 4 and 6 months of treatment. We assumed that the risk of relapse for patients in the 6-month arm was 3.5% (20–22) and that an absolute difference of 5% (i.e., relapse rate of 8.5%) was clinically meaningful. For a level of significance of 0.05 and 80% power (two-sided), we estimated that 284 evaluable subjects per arm were required.

We analyzed data using SAS 9.13 (SAS, Cary, NC). Parametric or nonparametric methods, as appropriate, were used to evaluate baseline characteristics. The primary endpoint was the proportion of subjects who relapsed. Equivalence was considered to be established if the confidence intervals for the difference in the binomial proportions with relapse obtained in the primary per-protocol and secondary intention-to-treat analyses fell within the specified equivalence range. The Hauck-Anderson correction (23, 24) was used. Kaplan-Meier estimates of relapse rates were obtained. We evaluated factors associated with relapse using univariate and multivariate Cox proportional hazards regression with inclusion of covariates guided by the likelihood-ratio test and based on backward elimination. Variables with $P < 0.05$ were considered for inclusion. Secondary endpoints of rate of relapse at 1 and 2 years were analyzed using Poisson regression.

RESULTS

Subjects were recruited from persons with suspected TB and patients with newly diagnosed pulmonary TB referred from public and private clinics to the Uganda-CWRU Research Collaboration TB Project Clinic, Mulago Hospital, Kampala, Uganda; the Federal University of Espírito Santo-Núcleo de Doenças Infecciosas, Vitória, Brazil; and the Tropical Diseases Foundation – Makati Medical Center, Makati City, Philippines. A total of 2,339 subjects were screened from April 2002 to August 2007. Patient flow and drop-outs are shown in Figure 1. After review of the results of their pretreatment drug susceptibility testing and the results of their sputum cultures after 2 months of treatment, 394 eligible patients with culture-confirmed pulmonary TB (61% male, mean age 31 years, 64% smear positive) were randomly assigned to complete 4 or 6 months of anti-TB treatment. Baseline characteristics were similar between patients in both study arms (Table 1). Several baseline characteristics differed between patients enrolled at the three sites (Table 2).

Due to an apparent increase in the proportion of subjects in the 4-month arm who relapsed, the Data and Safety Monitoring Board recommended stopping enrollment on August 30, 2007. All subjects being screened and those awaiting enrollment were treated with 6 months of standard short-course chemotherapy. All subjects were informed of the Board's recommendations and continued in follow-up.

A total of 185 subjects (94%) in the 4-month arm and 185 subjects (93%) in the 6-month arm completed study follow-up or developed recurrent TB. Follow-up rates did not differ between treatment arms. None of subjects in the 4-month arm failed treatment. Fourteen subjects enrolled in the 4-month arm and four subjects enrolled in the 6-month arm developed recurrent TB. Thirteen, 5, and 0 subjects developed recurrent TB at the Ugandan, Brazilian, and Philippines sites during follow-up, respectively. All recurrences were bacteriologically confirmed. The median time from the end of treatment until recurrent TB was 5.0 months (interquartile range, 8.9 months; range, 4.2–24 months).

Comparison of IS6110 DNA fingerprint patterns of pretreatment and recurrent isolates showed that 16 of 18 (89%) patients relapsed with their initial isolate and two subjects had recurrence due to exogenous reinfection with an MTB isolate different from their pretreatment isolate. One subject with exogenous reinfection was enrolled in Uganda in the 6-month treatment arm, and the other was enrolled in Brazil in the 4-month treatment arm. Subjects with exogenous reinfection were excluded from the relapse analysis. Of the 16 patients who relapsed, 10 (5.1%) subjects in the 4-month arm relapsed and three (1.5%) subjects in the 6-month arm relapsed within 1 year of completing anti-TB treatment. Three (1.5%) of subjects in the 4-month arm relapsed, and no subjects in the 6-month arm relapsed between 1 and 2 years of completing anti-TB treatment. The 1- and 2-year incidence rate ratios of relapse were 3.43 ($P = 0.061$) and 4.52 ($P = 0.018$), respectively (Table 3). All subjects relapsed with fully drug-susceptible TB and were successfully retreated.

The 95% confidence intervals with Hauck-Anderson correction for the difference in the binomial proportions with relapse did not fall within the protocol-specified equivalence range of 0 to 8.5% among the 370 patients included in the per-protocol analysis and among the 394 patients included in the intention-to-treat analysis (Table 3). The Kaplan-Meier analysis of the 386 patients completing assigned treatment and contributing any posttreatment follow-up time, with a cut-point of 30 months posttreatment follow-up, indicated a significant difference in relapse rates between the treatment arms (log-rank $\chi^2 = 6.57$; $P < 0.01$) (Figure 2). The results were similar when data were analyzed based on intention to treat.

Figure 1. Study profile. *Reasons for exclusion during screening (n): Cavitary disease (596), signs and symptoms not consistent with TB (410), HIV infected (344), extrapulmonary tuberculosis (TB) (82), serum aspartate aminotransferase over 1.5 upper limit of normal (82), refused directly observed treatment (DOT) (75), alcoholism, drug use or sex work (54), serum bilirubin over 1.3 mg/dl (51), hemoglobin less than 8 g/dl (37), random serum glucose more than 150 mg/dl (35), silicosis or chronic comorbidity (27), prior TB or TB treatment (22), serum creatinine more than 2 mg/dl (17), pregnant or breastfeeding (11), not ambulatory (7), exposure to MDR TB (5), receiving steroids (5). Categories not exclusive. [†]DOT. [‡]Reasons for exclusion before randomization (n): TB not culture confirmed (277), drug-resistant TB (54), unwilling to continue on DOT (50), nonadherence to study schedule (76), positive 2-month culture (29), incomplete DOT or incomplete treatment (6), pregnant (6), HIV seropositive (2), serious illness contraindicating enrollment (1), eligibility criteria not confirmed (1), enrollment suspended by DSMB before randomization (64). Categories not exclusive.

In univariate Cox proportional regression analyses of all patients who completed assigned treatment and contributed any posttreatment follow-up time, relapse was associated with treatment duration, site of enrollment, greater extent of disease on initial chest radiograph, higher baseline acid fast bacillus smear grade, lower baseline days to positive in liquid media, and lower baseline hemoglobin count (Table 4). When these factors were analyzed in a multivariate analysis using Cox regression, shortened treatment duration, enrollment at the Ugandan site, and extent of disease on baseline chest radiograph were independently associated with relapse (Table 5). When stratified by site, shortened treatment duration ($P < 0.03$) was associated with relapse at the Uganda site, whereas extent of disease on baseline chest radiograph ($P < 0.02$) was the only factor associated with relapse among patients enrolled at the Brazil site.

Safety

The number of subjects experiencing adverse events during anti-TB treatment was similar between the groups. Eighty-five grade 3 or 4 adverse events occurred during treatment and follow-up; 49

occurred among patients in the 4-month arm, and 36 occurred among patients in the 6-month arm ($P = 0.44$; χ^2). Two patients in each arm had study anti-TB treatment temporarily or permanently discontinued. Four deaths occurred during follow-up (two due to homicide, one due to malignant melanoma, and one due to acute myocardial infarction); all patients who died were in the 6-month treatment arm. All deaths were unrelated to study treatment as assessed by the local investigators.

DISCUSSION

In a randomized equivalence trial assessing whether TB treatment could be shortened in patients with noncavitary TB who converted their sputum cultures to negative after 2 months of treatment, we found that the proportion of patients who relapsed was significantly greater among those in the 4-month arm (7.0 vs. 1.6%, risk difference, 0.054; 95% CI with Hauck-Anderson correction, 0.01–0.10). Our trial was an international multicenter study conducted at sites in Brazil, the Philippines, and Uganda, three countries with a high burden of TB. At least

TABLE 1. BASELINE CHARACTERISTICS OF ENROLLED PATIENTS BY STUDY ARM (N = 394)*

Baseline Characteristics	4-Month Arm (n = 196)	6-Month Arm (n = 198)
Male, n (%)	119 (61)	120 (61)
Age, yr	31.2 (10)	30.3 (10)
Weight, kg	55.8 (10)	55.2 (10)
Body mass index, kg/m ²	20.6 (3)	20.3 (3)
Hemoglobin, g/dl	13.2 (2)	13.4 (2)
Chest radiograph—extent of disease, [†] n (%)		
Normal to minimal disease	77 (39)	91 (46)
Moderately advanced disease	94 (48)	91 (46)
Far advanced disease	25 (13)	16 (8)
Bilateral disease on chest radiograph	85 (43)	70 (35)
Highest sputum AFB smear grade, n (%)		
Negative	74 (38)	67 (34)
1+ to 2+	43 (22)	56 (28)
3+ to 4+	79 (40.3)	75 (37.9)
Time after inoculation in liquid media until positive sputum culture, d	11.0 (7)	10.0 (7)

Definition of abbreviation: AFB = acid fast bacillus.

* Values are mean (SD) unless otherwise noted.

[†] According to the scheme of the U.S. National Respiratory and Disease Association (25).

5 of 7 weekly doses were directly supervised, and the long-term follow-up rate for study endpoints was excellent at all sites.

Our trial had several limitations. First, enrollment was stopped early, and the number of patients enrolled was one half of the original sample size. However, follow-up rates were high, and a significant difference between the proportion of patients who relapsed in the treatment groups was present at the end of follow-up. The trial was an open-label study with possible assessment bias, but the primary study endpoints were based on bacteriology, and laboratory staff were blinded to treatment assignment. Standard procedures were used to evaluate patients with signs

TABLE 2. BASELINE CHARACTERISTICS OF ENROLLED PATIENTS BY SITE OF ENROLLMENT*

Baseline Characteristics	Uganda (n = 137)	Brazil (n = 162)	Philippines (n = 95)	Total (n = 394)
Male, n (%)	81 (59)	98 (60)	60 (63)	239 (61)
Age, yr [†]	27.4 (8)	34.1 (11)	29.9 (10)	30.8 (10)
Weight, kg [†]	55.6 (8)	57.9 (9)	51.2 (11)	55.5 (10)
Body mass index, kg/m ² [‡]	20.1 (3)	21.0 (3)	20.0 (3)	20.4 (3)
Hemoglobin, g/dl [†]	12.9 (2)	13.3 (1)	14.0 (2)	13.3 (2)
Chest radiograph—extent, [§] n (%)				
Normal to minimal disease	46 (33)	48 (30)	74 (78)	168 (43)
Moderately advanced disease	82 (60)	86 (53)	17 (18)	185 (47)
Far advanced disease	9 (7)	28 (17)	4 (4)	41 (10)
Bilateral disease on chest radiograph	43 (31)	77 (48)	35 (37)	155 (39)
Highest sputum AFB smear grade, n (%) [¶]				
Negative	5 (3)	73 (45)	63 (66)	141 (36)
1+ to 2+	42 (31)	36 (22)	21 (22)	99 (25)
3+ to 4+	90 (66)	53 (33)	11 (12)	154 (39)
Time after inoculation until positive sputum culture in liquid media, d [†]	7.7 (7)	9.9 (6)	13.4 (7)	11.2 (7)

Definition of abbreviation: AFB = acid fast bacillus.

* Values are mean (SD) unless otherwise noted.

[†] Kruskal-Wallis test for overall difference among sites ($P < 0.001$).

[‡] Kruskal-Wallis test for overall difference among sites ($P < 0.002$).

[§] According to the scheme of the U.S. National Respiratory and Disease Association (25).

[¶] Chi-square test for overall difference among sites ($P < 0.001$).

TABLE 3. BINOMIAL PROPORTIONS OF RELAPSE AND SECONDARY ENDPOINTS

Endpoints	n	4-Month Arm	6-Month Arm	Risk Difference	95% CI*
Primary endpoint					
Binomial proportion of relapse (intention-to-treat)	394	13/196 (6.6%)	3/198 (1.5%)	0.051	0.01–0.09
Binomial proportion of relapse (per-protocol)	370	13/185 (7.0%)	3/185 (1.6%)	0.054	0.01–0.10
Secondary endpoints [†]				Incident rate ratio	
Rate of relapse at 1 yr [‡]	386	10/2218 (4.51)	3/2284 (1.31)	3.43	0.94–12.5
Rate of relapse at 2 yr [‡]	386	13/4310 (3.02)	3/4500 (0.67)	4.52	1.29–15.9

* Confidence interval for difference of binomial proportions adjusted with Hauck-Anderson continuity correction.

[†] Includes all patients who were adherent with treatment and contributed posttreatment follow-up within the time period of interest.

[‡] Number of events/ person-months (rate per 1,000 person-months).

and symptoms suggestive of recurrent TB, two independent experts reviewed cases of recurrent TB, and all relapses were bacteriologically confirmed. Culture conversion after 2 months of treatment was based on cultures on solid media, which are less sensitive than enriched liquid media. However, the original studies on which the correlation of 2-month culture status and relapse is based were done with traditional solid media, which are the most widely used culture media worldwide. The use of plain or computed chest tomography is more sensitive than posteroanterior radiographs for the detection of cavitory disease. We based study eligibility on standard posteroanterior radiographs because this is the examination used by TB control programs and was the method used in previous studies demonstrating an association between cavitory disease and sputum bacillary load and risk for relapse. Similarly, chest radiographs were interpreted by chest physicians rather than a central reader because this was a pragmatic trial and replicates how chest radiographs are routinely reviewed in TB programs throughout the world.

Number at Risk

6 Month Arm	193	193	191	190	187	184	182
4 Month Arm	193	193	192	181	178	174	173

Figure 2. Kaplan Meier curve showing the cumulative percentage of patients who relapsed after completing anti-tuberculosis (TB) treatment. The chi-square test for a difference in the percentage of patients who relapsed by treatment arm was significant ($P < 0.01$). Error bars represent the standard error of the mean percentage of patients who relapsed at 6, 12, and 24 months of follow-up after completing treatment.

TABLE 4. UNIVARIATE COX PROPORTIONAL HAZARD OF RISK FACTORS OF RELAPSE IN PATIENTS COMPLETING ASSIGNED INTERVENTION AND CONTRIBUTING ANY POSTTREATMENT FOLLOW-UP TIME

Potential Risk Factors	n	Unadjusted HR	95% CI	P Value
Shortened treatment (4-mo arm)	386	4.47	1.27–15.68	0.019
Site of enrollment	386			
Uganda		3.6	1.16–11.16	0.027
Philippines		0	0	0.99
Brazil (reference)*		1	—	—
Age, yr	386	0.98	0.93–1.04	0.562
Male sex	386	1.09	0.40–3.00	0.867
Weight, kg	386	1.03	0.98–1.08	0.242
Body mass index, kg/m ² †	386	0.95	0.80, 1.14	0.597
Hemoglobin, mg/dl†	386	0.71	0.53–0.95	0.0197
Extent of disease on chest radiograph†	386			
Far advanced		7.47	1.78–31.26	0.006
Moderately advanced		2.47	0.66–9.30	0.182
Minimal to none (reference)		1	—	—
Bilateral disease on chest radiograph†	386	1.59	0.60–4.22	0.3569
AFB smear grade†	386			
Grade 3+ to 4+		11.15	1.45–85.79	0.021
Grade 1+ to 2+		4.17	0.43–40.09	0.216
Negative (reference)		1	—	—
Time after inoculation in liquid media until positive sputum culture‡	377	0.81	0.69–0.94	0.007
More than 5% weight gain at end of intensive phase	386	1.36	0.47–3.92	0.568

Definition of abbreviations: AFB = acid fast bacillus; CI = confidence interval; HR = hazard ratio.

* The Brazil site was used as the reference group for the comparison of relapse risk by site of enrollment.

† Baseline (pretreatment) value.

‡ For multiple specimens, the lowest value for each patient was used; nine patients had missing results.

Relapse rates were higher in Uganda and Brazil than at the Philippines site. Eligibility criteria were identical for all sites; however, the radiographic extent of disease (no cavitary disease but more lung fields involved by any tuberculous lesions) was greater in Uganda, and the time to positive liquid culture, a measure of initial sputum bacillary load (26), was higher in Uganda. No patients relapsed with TB at the Philippines site where radiographic lesions were less profuse and the initial sputum bacillary load was lower.

In our study, treatment with 4 months (112 doses) of current, first-line, anti-TB drugs delivered by directly observed treatment was inadequate to sterilize pulmonary tissues in patients with noncavitary TB who converted their sputum cultures to

TABLE 5. MULTIVARIATE COX PROPORTIONAL HAZARD OF RISK FACTORS* FOR RELAPSE FOR PATIENTS COMPLETING ASSIGNED INTERVENTION AND CONTRIBUTING ANY POSTTREATMENT FOLLOW-UP TIME (N = 386)

Potential Risk Factors	Adjusted HR	95% CI	P Value
Shortened treatment (4-mo arm)	4.14	1.17–14.63	0.0273
Ugandan site of enrollment	6.83	2.18–21.35	0.0010
Far advanced extent of disease on baseline chest radiograph	4.92	1.69–14.36	0.0035

Definition of abbreviation: CI = confidence interval; HR = hazard ratio.

* Covariates included for consideration in the model but backward eliminated based on a selection criteria of *P* less than 0.05 were male sex, baseline age, moderately advanced extent of disease, acid fast bacillus smear grade, treatment arm by Uganda site interaction, body mass index, hemoglobin, and time after inoculation in liquid media until positive sputum culture.

negative during the intensive phase of therapy. Sixty-two dose regimens administered thrice weekly for 6 months have been shown to be highly effective in smear-positive adults with radiographically advanced forms of TB (20). Why is the duration of treatment more important than more doses in achieving durable cure? Failure to eradicate persistent tubercle bacilli that are metabolically less active or dormant and, therefore, resistant to (27) or only susceptible to killing by drugs intermittently is believed to be the basis for a biological basis for relapse (28, 29). The probability of eliminating all persistent organisms is likely determined by the dose, rhythm, mechanism of action of the drugs used, and duration of therapy. Findings from this trial are consistent with the special populations hypothesis whereby different populations of tubercle bacilli, perhaps in different types of pulmonary lesions, are metabolically active or dormant (30, 31). If so, successful strategies to shorten TB treatment need to focus on optimized doses of current drugs or the introduction of new drugs with novel mechanisms of action. Clinical trials with higher doses of rifampin and rifapentine and studies of new compounds such as TMC-207, a diarylquinoline that inhibits mycobacterial ATP synthase (32), and OPC67883, a nitro-dihydro-imidazo-oxazole that inhibits mycolic acid synthesis (33), are underway and should help address these questions.

Our study demonstrates the limitations of using one or a few of the current clinical and bacteriologic endpoints, such as the presence of cavities and 2-month culture conversion, as predictors of individual treatment outcomes. Although useful surrogate biomarkers, similar to CD4 lymphocyte counts and viral load in HIV treatment, are greatly needed to expedite TB drug development and testing and patient care, a surrogate such as 2-month culture conversion may not be useful in all settings or with different drugs and regimens. Surrogate markers and predictors need careful validation in phase 3 clinical trials in comparison with standard treatment outcomes such as relapse (34). The combination of noncavitary disease and 2-month culture conversion was not sufficient to identify patients with TB with decreased risk for relapse.

In conclusion, shortening treatment from 6 to 4 months in adults with noncavitary disease and sputum culture conversion after 2 months of treatment resulted in significantly more relapses among those treated for 4 months. Better biomarkers, optimized dosing of current drugs, and drugs with novel mechanisms of action are needed to further shorten TB treatment. Until new drug regimens are available, novel biomarkers combined with clinical and microbiological parameters are likely the only means to identify patients, along the continuum of *M. tuberculosis* disease, who may benefit from shortened TB treatment.

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