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The Association between Symptoms and Microbiologically Defined Response to Tuberculosis Treatment

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Abstract

Rationale—The lack of consistent associations between clinical outcomes and microbiological responses to therapy for some infectious diseases has raised questions about the adequacy of microbiological endpoints for tuberculosis treatment trials.

Objectives—To evaluate the association between symptoms and microbiological response to tuberculosis treatment.

Methods—We performed a retrospective analysis of four clinical trials in which participants had culture-positive tuberculosis, standardized symptom assessment, and follow-up mycobacterial cultures. Two trials (studies 22 and 23) followed participants to identify recurrent tuberculosis; participants in studies 27 and 28 were only followed to treatment completion.

Measurements and Main Results—This analysis included 1,978 participants; 39 (2.0%) had culture-confirmed treatment failure, and 75 (3.9%) had culture-confirmed recurrence. Productive cough was associated with indices of increased mycobacterial burden at diagnosis (acid-fast smear grade, severity of radiographic abnormalities). Fever and sweats improved rapidly with treatment, whereas productive cough decreased more slowly and was present in 20% of visits after treatment completion. During treatment, study participants with productive cough more often had concurrent culture positivity compared with those without productive cough (studies 22 and 23: adjusted odds ratio, 1.80; 95% confidence interval [CI], 1.33–2.44). Finally, symptoms during the latter part of

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treatment and follow-up were associated with culture-confirmed treatment failure and recurrence in studies 22 and 23 (for cough: adjusted hazard ratio, 2.07; 95% CI, 1.23–3.49; for fever: adjusted hazard ratio, 5.05; 95% CI, 2.76–9.19).

Conclusions—There are consistent relationships between symptoms and microbiological indices of tuberculosis, including measures of mycobacterial burden at baseline, culture positivity during treatment, and time to culture-confirmed treatment failure and recurrence.

Keywords

tuberculosis; drug treatment; treatment failure; recurrence; cough

The field of tuberculosis (TB) treatment has emphasized bacteriological outcomes of therapy for several decades (1). The traditional endpoints for clinical trials of TB treatment have been treatment failure (sputum culture-positivity at or near the end of treatment) and recurrent disease (culture positivity after the completion of treatment). However, a recent review of the literature by the Food and Drug Administration revealed a lack of recent attention to the association between these microbiologically defined outcomes of TB treatment and the symptoms of TB (2). The lack of consistent associations between clinical and microbiologically defined responses to therapy in other infectious diseases (e.g., otitis media, bacterial pneumonia [3, 4]) raises questions about the adequacy of microbiological endpoints for TB treatment trials.

Previous studies have established that quality of life is decreased in patients with TB and improves with treatment (5–8). Residual symptoms and pulmonary impairment have been reported among patients with microbiologically cured pulmonary TB (9, 10), presumably reflecting damage to the lungs that occurred before control of the infection or because of concomitant lung disease. Results from these studies are limited because they did not include an assessment of participants in clinical trials and did not compare symptoms with microbiological response to treatment. We used results from four clinical trials performed by the Tuberculosis Trials Consortium (TBTC) to evaluate the association between symptoms and concurrent microbiological status before, during, and after treatment.

Materials and Methods

The TBTC has used a standard set of questions to assess the presence of common symptoms of TB: fever; sweats (soaking clothes or sheets); cough; and, if present, whether the cough is productive. Symptoms and body weight were assessed at enrollment, every 2 to 4 weeks during treatment, every 3 to 6 months during follow-up to detect recurrent TB, and at the time of suspected treatment failure or recurrence. The severity of these symptoms was not uniformly assessed in these studies. Detailed information on the demographic and clinical characteristics of the patients included and for definitions used throughout the analysis is provided in the online supplement.

The four clinical trials used for this analysis were limited to patients with culture-positive TB who were treated using directly observed therapy (Table 1) (11–15). Two trials (studies 22 and 23, conducted in the United States and Canada) were chosen because they included

follow-up after completion of therapy to detect recurrent TB. Furthermore, study 23 evaluated TB treatment for patients with HIV coinfection. Studies 27 and 28 (conducted in the United States, Uganda, South Africa, Brazil, and Spain) were included because they included frequent study visits during the first 2 months of therapy and provided additional cases of treatment failure. However, patients were not followed beyond the end of treatment; hence, these trials cannot be used for analyses of the relationship between symptoms and recurrent TB.

Microbiological Techniques and Outcome Definitions

All four trials used both liquid and solid culture media results at each time point to determine microbiological outcomes. If either media type was positive for growth of *Mycobacterium tuberculosis*, the sputum culture was considered positive for that time point. "Treatment failure" was defined as a positive culture at or beyond 4 months of therapy but before its completion. "Recurrent tuberculosis" was defined as a positive culture after the completion of therapy and during 18 months of follow-up (Table 1). Paired baseline and failure/recurrence isolates underwent DNA fingerprinting. Though uncommon in these studies, three cases of apparent reinfection were included in this analysis (16).

Data Analysis

We used several methods to evaluate the association between symptoms and concurrent microbiological status before, during, and after treatment, including contingency tables, graphical summaries, regression with correlated data, and time to event.

We used contingency tables with Pearson's chi-squared test to evaluate the association between symptoms at baseline and the following measures of the mycobacterial burden at baseline at or very near the initiation of treatment: sputum smear grade (high bacillary load was defined as $\geqslant 1$ acid-fast bacilli/field at 1,000×) and the severity of chest radiographic abnormalities.

We used graphical methods to depict the change in frequency of symptoms and culture positivity over the first 24 weeks after starting therapy. We evaluated the association between concurrent symptoms and positive sputum cultures during therapy using logistic regression analysis with generalized estimating equations to compensate for statistical dependence among multiple observations on individuals (17) (additional details are provided in the online supplement).

We used Cox proportional-hazard regression models to quantify the association of time to treatment failure or recurrence with concurrent symptoms. We assessed potential confounding by study and HIV status. Because the frequency of study visits differed, we performed all of these analyses separately for studies 22 and 23 and then for studies 27 and 28. Statistical analyses were performed using SAS (version 9.2; SAS Institute, Inc., Cary, NC) and R (version 2.10.1; The R Foundation for Statistical Computing) (18).

Results

TBTC studies 22, 23, 27, and 28 collectively enrolled 2,025 patients (Table 2). Of these, 27 patients had baseline cultures that were either negative or grew drug-resistant *M. tuberculosis*; these patients were discontinued from study therapy and not included in this analysis. The median age of the remaining cohort of 1,998 patients was 38.5 years (interquartile range 29, 49 yr), 73% were male, and 18% had HIV coinfection. Of the 1,998 patients in the analysis, 39 had culture-confirmed treatment failure, and 75 had culture-confirmed recurrence.

Association between Symptoms and Mycobacterial Burden at Baseline

Productive cough was more common among patients with high-grade sputum smear or pulmonary cavitation in studies 22, 27, and 28 (those studies with consistently collected baseline data) (Table 3). For example, in studies 27 and 28, 94% (450/480) of patients whose sputum had high-grade smear positivity had productive cough, compared with 86% (198/230) of patients whose sputum smear grade was less than 1 bacillus per high-power field ($P < 0.001$). The relationship between fever and sweats and measures of mycobacterial burden was less consistent, with a significant association in study 22 but not in studies 27 and 28.

Change in Symptoms during Treatment

Fever and sweats improved rapidly with treatment (Figures 1A and 1B). By 6 to 8 weeks of treatment, fewer than 10% of patients had either of these symptoms. The prevalence of productive cough decreased steadily with treatment but was present in 35 to 50% of study patients at Week 8 of therapy (Figure 1C). Thereafter, the prevalence of productive cough remained at approximately 20% during or after therapy. For all three symptoms, the curves of the decrease in prevalence of symptoms were similar across studies. Sputum culture positivity declined steadily in the first 12 weeks of therapy, and very few patients had positive cultures at or after 16 weeks (Figure 1D).

Association between Symptoms and Mycobacterial Burden at Week 8 of Treatment

We initially focused on the 8-week time point, given the use of sputum culture status at that time point as a surrogate marker of the sterilizing effect of a therapeutic regimen (19). Productive cough at Week 8 was more common among patients with a positive sputum culture (Table 4). For example, in study 22, productive cough was present in 51% of those with a positive 8-week culture, compared with 29% of those with a negative culture ($P < 0.001$). Furthermore, productive cough was consistently associated with high sputum smear grade. The association between productive cough and radiographic measures of disease severity was less consistent, being present in study 22 but not in studies 27 and 28. Fever and sweats were uncommon at Week 8 and showed no significant association with measures of mycobacterial burden (data not shown).

Association between Symptoms and Concurrent Culture Positivity over the Course of Treatment

We used logistic regression analysis with generalized estimating equations to evaluate the association between productive cough and concurrent sputum culture positivity at any point during treatment. In an initial bivariate analysis adjusting for time on treatment, study participants with cough had twice the odds of having concurrent sputum culture positivity (studies 22 and 23: odds ratio [OR], 2.23; 95% confidence interval [CI], 1.70–2.92; studies 27 and 28: OR, 2.27; 95% CI, (1.90–2.72) (Tables 5 and 6). These odds ratios were minimally attenuated (studies 22 and 23: adjusted OR, 1.80; 95% CI, 1.33–2.44 [$P < 0.001$]; studies 27 and 28: OR, 1.71; 95% CI, 1.41–2.07 [$P < 0.001$]) in multivariate models adjusting for factors that have previously been associated with treatment outcome (being underweight at diagnosis, weight change in the first 8 weeks of treatment, baseline bacillary load on sputum smear, bilateral and cavitary disease on chest radiography at baseline, HIV status, and enrollment at an African site [studies 27 and 28]).

Association between Symptoms and Culture-Confirmed Treatment Failure or Recurrence

Of the 89 patients who experienced culture-positive treatment failure or recurrence in studies 22 and 23, 85 (96%) had concurrent information on symptoms. Of these 85 participants, 56 (66%) had at least one symptom at the time of culture-confirmed treatment failure or recurrence. An additional 1,156 participants did not experience treatment failure or relapse and had symptom information at Week 16 or later. Fever (hazard ratio [HR], 5.68; 95% Wald CI, 3.15–10.24 [$P < 0.001$]) and productive cough (HR, 2.58; 95% CI, 1.58–4.22 [$P = 0.002$]) were associated with culture-confirmed treatment failure or recurrent TB (Table 7). These associations attenuated only slightly when adjusted for other factors previously shown to be associated with treatment failure or recurrence in study 22 (11). In studies 27 and 28, 25 participants experienced treatment failure, and an additional 666 participants with symptom information between Weeks 12 and 24 did not experience treatment failure. Productive cough was associated with culture-positive treatment failure (HR, 4.70; 95% CI, 2.11–10.47 [$P < 0.001$]). None of the patients with treatment failure reported fever or sweats between Weeks 12 and 24. Because there were few visits at risk for treatment failure, we did not construct a multivariate hazard regression model for studies 27 and 28.

Discussion

Using data from four prospective clinical trials, we have shown consistent relationships between symptoms and microbiological outcomes of TB treatment. Symptoms were more common among patients with a greater burden of *M. tuberculosis* at the time of diagnosis. During treatment, the presence of concurrent productive cough was consistently associated with sputum culture positivity, including in models that adjusted for other factors that have been associated with disease severity. Finally, symptoms (productive cough and fever) were associated with the two microbiological outcomes that have been used in clinical trials over the past 40 years: culture-confirmed treatment failure and recurrence. Although there were minor differences in these associations in different clinical trials, the consistency in the response of symptoms to treatment and the consistency of the associations with culture positivity during treatment are impressive.

Our results are similar to data from a clinical trial done in Uganda, Brazil, and the Philippines (20). In that study of 394 HIV-negative patients with culture-positive pulmonary TB, symptoms were associated with measures of mycobacterial burden at baseline, and symptoms improved quickly with therapy. Furthermore, symptoms (fever, cough, and chest pain) were more common at the time of recurrent culture positivity (microbiologic recurrence) than among patients who had negative cultures during follow-up.

The United States Food and Drug Administration is charged with assuring that new medications are both safe and effective. Demonstration of effectiveness requires improvement in how the patient feels, functions, or survives. The relationship between clinical symptoms and microbiological indices of TB had not been emphasized in clinical trials over the past 40 years, and the resultant lack of data has led to questions about the validity of sputum culture as an appropriate surrogate endpoint for licensure of new drugs.

Appropriate concerns have been raised about using microbiological culture as the primary outcome of treatment trials for infectious diseases such as otitis media; there is a weak relationship between conversion of cultures to negative and the clinical outcomes of such treatment (4). TB has several factors that make it quite different from bacterial pneumonia and similar acute bacterial infections. First, the pathogens that commonly cause acute bacterial infections (e.g., *Streptococcus pneumoniae*) can be commensal bacteria; therefore, culture positivity from cultures of nonsterile sites (e.g., sputum) at baseline or during treatment may represent colonization. In contrast, *M. tuberculosis* is not a commensal bacterium, so its presence in a culture is nearly always associated with disease (if laboratory cross-contamination has been ruled out). Furthermore, we have shown consistent relationships between symptoms of TB and a number of microbiological outcomes of therapy.

Despite the consistent relationship between productive cough and microbiological outcome of TB treatment, cough would be a problematic endpoint for TB treatment. Productive cough was present in approximately 20% of patients at any time point during the latter part of treatment and during follow-up after completion of therapy. It is likely that residual cough after microbiologically successful treatment represents residual pulmonary damage from TB, conditions associated with cough and risk for TB (e.g., tobacco use or silicosis), and/or other pulmonary diseases (e.g., asthma). However, the consistent relationship between productive cough and culture positivity demonstrates that it is appropriate to use microbiologically defined endpoints as the primary endpoints for TB treatment trials (21).

This study had at least four limitations. First, our analyses were limited to symptoms and other clinical features that were consistently measured across all four studies. Because the severity of symptoms was not uniformly recorded, we were not able to analyze the relationship between symptom severity and microbiological findings. Second, the four studies did not uniformly collect data on other potential causes of cough, such as tobacco use or history of specific pulmonary diseases, such as obstructive pulmonary disease or asthma. Third, mycobacterial culture techniques were not standardized other than requiring that specimens be cultured in a certified lab and include use of approved broth and solid

culture media. Finally, only two of the four studies included in this analysis followed patients for recurrent TB, limiting the power of this key association.

Conclusions

There are consistent relationships between symptoms and microbiological indices of TB, including measures of mycobacterial burden at baseline, culture positivity during treatment, and culture-confirmed treatment failure and recurrence. These consistent relationships demonstrate that the use of microbiological outcomes is appropriate in clinical trials of new agents for TB treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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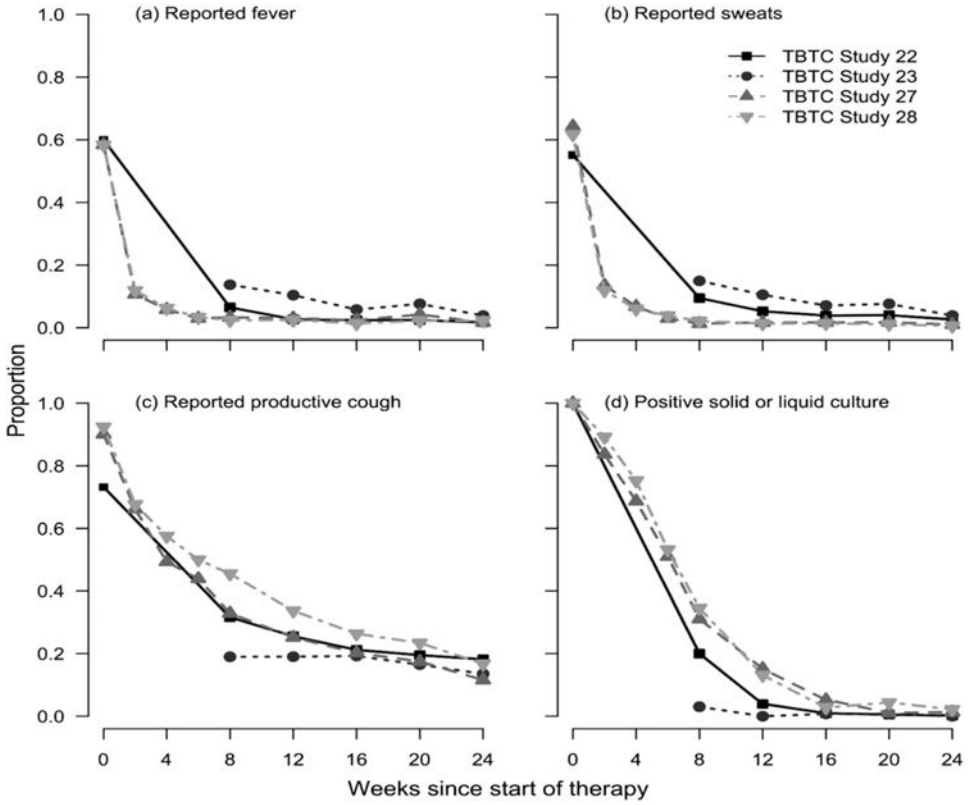

Figure 1.

Frequency of fever (*A*), sweats (*B*), productive cough (*C*), and culture positivity (by solid or liquid culture) (*D*) during Weeks 0 to 24 after initiation of tuberculosis treatment among patients in Tuberculosis Trials Consortium (TBTC) Studies 22, 23, 27, and 28. Study 23 data are not included for Week 0 because enrollment occurred after the beginning of treatment.

Table 1

Key features of the Tuberculosis Trials Consortium clinical trials included in this analysis

Trial	Study Population	Intervention Evaluated	Time of Enrollment	Timing of Study Visits at which Symptoms Were Assessed	Primary Endpoint	Duration of Follow-up
Study 22 (11, 12)	Pulmonary TB, susceptible to INH and RIF	Once-weekly rifapentine plus INH vs. twice-weekly rifampin plus INH in the continuation phase	2 mo (end of the intensive phase of therapy)	Time of TB diagnosis (retrospectively); monthly during Months 2–6 of treatment, then at 3, 6, 9, 12, 18, and 24 mo after completing treatment	Culture-positive treatment failure or recurrent TB	24 mo after completing treatment
Study 23 (15)	Pulmonary or extrapulmonary TB, susceptible to RIF	Twice-weekly rifabutin plus INH in the continuation phase	At any time during the first 2 mo of treatment	Monthly during months 2–6 of treatment, then at 3, 6, 9, 12, 18, and 24 mo after completing treatment	Culture-positive treatment failure or recurrent TB	24 mo after completing treatment
Study 27 (13)	Smear-positive pulmonary TB, susceptible to RIF	Moxifloxacin vs. ethambutol (both in combination with INH, RIF, and PZA)	Within 7 d of starting TB treatment	Weeks 0, 2, 4, 6, and 8 and then monthly during the remainder of treatment	2-mo sputum culture status	Completion of TB therapy
Study 28 (14)	Smear-positive pulmonary TB, susceptible to INH and RIF	Moxifloxacin vs. INH (both in combination with RIF, PZA, and EMB)	Within 7 d of starting TB treatment	Weeks 0, 2, 4, 6, and 8 and then monthly during the remainder of treatment	2-mo sputum culture status	Completion of TB therapy

Definition of abbreviations: EMB = ethambutol; HIV = human immunodeficiency virus; INH, isoniazid; PZA = pyrazinamide; RIF = rifampin; TB = tuberculosis.

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Table 2

Number of patients included in the analysis and the number of microbiologically defined treatment endpoints

Trial	Enrolled Number	Number Included in this Analysis	HIV Coinfection, n (%)	Treatment Failure, n (%)	Recurrence, n (%)
Study 22	1,075	1,075	71/1075 (6.6)	11/1,075 (1.0)	69/1,075 (6.6)
Study 23	181	181	181/181 (100)	3/181 (1.7)	6/181 (3.3)
Study 27	336	322	71/322 (22.0)	11/322 (3.3)	not assessed
Study 28	433	420	45/420 (10.7)	14/420 (3.2)	not assessed
Total	2,025	1,998	368/1,998 (18.4)	39/1,998 (2.0)	75/1,256 (6.1)

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Table 3

Associations between symptoms and sputum smear grade and radiographic indices of disease severity at the time of tuberculosis treatment initiation (week 0) among patients in Tuberculosis Trials Consortium Studies 22, 27, and 28

Study	Index of Severity	Fever		Sweats		Productive Cough	
		n (%)	*P* Value	n (%)	*P* Value	n (%)	*P* Value‡
22*(n = 1,075)†	Smear grade						
	Smear ⩾ 1 per high power field	317/427 (74)		302/426 (71)		378/438 (86)	
	Smear < 1 per high power field	278/570 (49)	<0.001	243/565 (43)	<0.001	362/577 (63)	<0.001
	Chest radiographic features						
	Cavitation	307/463 (66)		286/460 (62)		394/475 (83)	
	No cavitation	275/522 (53)	<0.001	250/518 (48)	<0.001	341/527 (65)	<0.001
	Bilateral abnormalities	348/530 (66)		330/524 (63)		427/539 (79)	
	Unilateral abnormalities or normal	272/501 (54)	<0.001	239/501 (48)	<0.001	343/509 (67)	<0.001
27 and 28 (n = 742)	Smear grade						
	Smear ⩾ 1 per high power field	276/480 (58)		296/480 (62)		450/480 (94)	
	Smear < 1 per high power field	140/230 (61)	0.39	152/230 (66)	0.25	198/230 (86)	<0.001
	Chest radiographic features						
	Cavitation	313/545 (57)		342/545 (63)		510/545 (94)	
	No cavitation	120/197 (61)	0.40	124/197 (63)	0.96	168/197 (85)	<0.001
	Bilateral abnormalities	249/424 (59)		281/424 (66)		391/424 (92)	
	Unilateral abnormalities or normal	184/318 (58)	0.81	185/318 (58)	0.02	287/318 (90)	0.35

*Study 22 only because enrollment in Study 23 occurred after beginning of treatment.

†Missing values for symptoms, smear grade, or chest radiographic features may reduce denominator totals.

‡*P* value for Pearson's chi-squared test.

Table 4

Associations between productive cough and culture results, sputum smear grade, and radiographic indices of disease severity at 8 weeks of therapy among patients in Tuberculosis Trials Consortium Studies 22, 23, 27, and 28

Study	Laboratory and Radiographic Features of Tuberculosis	Percent Reporting Productive Cough, n (%)	*P* Value*
22 and 23 (n = 1,246)†	Sputum culture result		
	Positive	103/208 (50)	
	Negative	261/971 (27)	<0.001
	Smear grade		
	Smear ⩾ 1 per high-power field	24/35 (69)	
	Smear < 1 per high-power field	339/1,135 (30)	<0.001
	Chest radiographic features		
	Cavitation	161/394 (41)	
	No cavitation	186/766 (24)	<0.001
	Bilateral abnormalities	205/574 (36)	
	Unilateral abnormalities or normal	159/613 (26)	<0.001
27 and 28 (n = 742)†	Sputum culture result		
	Positive	114/207 (55)	
	Negative	144/417 (35)	<0.001
	Smear grade		
	Smear ⩾ 1 per high-power field	36/44 (82)	
	Smear < 1 per high-power field	219/571 (38)	<0.001
	Chest radiographic features		
	Cavitation	203/506 (40)	
	No cavitation	69/175 (39)	0.89
	Bilateral abnormalities	170/386 (44)	
	Unilateral abnormalities or normal	102/295 (35)	0.01

**P* value for Pearson's chi-squared test.

†Missing values for symptoms, smear grade, or chest radiographic features may reduce denominator totals.

Table 5

Partially and fully adjusted models of the association between the presence of symptoms and concurrent culture positivity during tuberculosis therapy in Tuberculosis Trials Consortium studies 22 and 23

Term	Partially Adjusted Model		Fully Adjusted Model	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Symptoms				
Productive cough	2.23 (1.70–2.92)	<0.001	1.80 (1.33–2.44)	<0.001
Fever	1.24 (0.74–2.07)	0.42	1.42 (0.77–2.63)	0.26
Sweats	0.64 (0.38–1.05)	0.078	0.70 (0.40–1.22)	0.21
Time on therapy *				
Weeks 8–16	0.65 (0.61–0.69)	<0.001	0.63 (0.59–0.68)	<0.001
Weeks 16–24	0.88 (0.77–1.01)	0.074	0.90 (0.78–1.04)	0.14
Weight †				
Underweight at diagnosis			1.54 (1.10–2.15)	0.011
Gained > 4 kg			1.14 (0.78–1.67)	0.50
Any weight loss			0.93 (0.56–1.54)	0.77
Missing weight change			1.79 (1.01–3.14)	0.045
Severity of disease at baseline				
Smear ⩾ 1 AFB/field at 1,000×			2.31 (1.64–3.24)	<0.001
Cavitary disease			2.75 (1.91–3.98)	<0.001
Bilateral disease			1.78 (1.25–2.53)	0.001
Other				
HIV positive			0.33 (0.16–0.66)	0.002

Definition of abbreviations: AFB = acid-fast bacilli; CI = confidence interval; OR = odds ratio.

*Time on therapy was modeled as two separate continuous variables, each with different slopes. The odds ratio represents weekly change in odds during the indicated time period since start of therapy.

†Weight change over Weeks 0 to 8, with a gain 0–4 kg as referent.

Table 6

Partially and fully adjusted models of the association between the presence of symptoms and concurrent culture positivity during tuberculosis therapy in Tuberculosis Trials Consortium studies 27 and 28

Term	Partially Adjusted Model		Fully Adjusted Model	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Symptoms				
Productive cough	2.27 (1.90–2.72)	<0.001	1.71 (1.41–2.08)	<0.001
Fever	1.26 (0.83–1.91)	0.28	1.25 (0.80–1.94)	0.33
Sweats	0.95 (0.66–1.38)	0.81	0.96 (0.63–1.46)	0.84
Time on therapy *				
Weeks 2–8	0.66 (0.63–0.68)	<0.001	0.60 (0.57–0.63)	<0.001
Weeks 8–16	0.75 (0.71–0.79)	<0.001	0.73 (0.70–0.77)	<0.001
Weeks 16–24	0.90 (0.82–1.00)	0.042	0.90 (0.82–0.99)	0.024
Weight †				
Underweight at diagnosis			1.22 (0.96–1.57)	0.11
Gained > 4 kg			0.88 (0.59–1.31)	0.53
Any weight loss			0.93 (0.58–1.48)	0.75
Missing weight change			0.81 (0.62–1.07)	0.14
Severity of disease at baseline				
Smear ⩾ 1 AFB/field at 1,000×			1.93 (1.49–2.51)	<0.001
Cavitary disease			1.85 (1.41–2.43)	<0.001
Bilateral disease			1.59 (1.25–2.03)	<0.001
Other				
African site			2.73 (2.05–3.64)	<0.001
HIV positive			0.67 (0.47–0.97)	0.032

Definition of abbreviations: AFB = acid-fast bacilli; CI = confidence interval; OR = odds ratio.

* Time on therapy was modeled as three separate continuous variables, each with different slopes. The odds ratio represents weekly change in odds during the indicated time period since start of therapy.

† Weight change over Weeks 0 to 8, with a gain of 0–4 kg as referent.

Table 7

Hazard regression analysis from Cox regression analysis of the association between the presence of symptoms and time to treatment failure or recurrence after week 12 in Studies 22 and 23

Term	Partially Adjusted Model		Fully Adjusted Model	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Symptoms				
Productive cough	2.58 (1.58–4.22)	<0.001	2.07 (1.23–3.49)	0.006
Fever	5.68 (3.15–10.24)	<0.001	5.04 (2.76–9.19)	<0.001
Sweats	1.61 (0.88–2.96)	0.12	2.26 (1.22–4.16)	0.009
Weight *				
Underweight at diagnosis			1.64 (1.03–2.59)	0.036
Gained > 4 kg			1.05 (0.64–1.71)	0.85
Any weight loss			0.60 (0.28–1.29)	0.19
Missing weight change			0.62 (0.24–1.60)	0.33
Severity of disease at baseline				
Smear ⩾ 1 AFB/field at 1,000×			1.22 (0.77–1.93)	0.39
Cavitary disease			3.34 (1.91–5.84)	<0.001
Bilateral disease			2.11 (1.25–3.56)	0.005
Other				
HIV positive			1.12 (0.58–2.17)	0.73

Definition of abbreviations: AFB = acid-fast bacilli; CI = confidence interval; OR = odds ratio.

* Weight change over Weeks 0 to 8, with a gain 0 to 4 kg as referent.