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ORIGINAL RESEARCH

Patient outcomes associated with post-tuberculosis lung damage in Malawi: a prospective cohort study

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2019-213808).

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Received 11 July 2019
Revised 9 December 2019
Accepted 29 January 2020

ABSTRACT

Background Post-tuberculosis lung damage (PTLD) is a recognised consequence of pulmonary TB (pTB). However, little is known about its prevalence, patterns and associated outcomes, especially in sub-Saharan Africa and HIV-positive adults.

Methods Adult (≥15 years) survivors of a first episode of pTB in Blantyre, Malawi, completed the St George's Respiratory Questionnaire, 6-minute walk test, spirometry and high-resolution CT (HRCT) chest imaging at TB treatment completion. Symptom, spirometry, health seeking, TB-retreatment and mortality data were collected prospectively to 1 year. Risk factors for persistent symptoms, pulmonary function decline and respiratory-related health-seeking were identified through multivariable regression modelling.

Results Between February 2016 and April 2017, 405 participants were recruited. Median age was 35 years (IQR: 28 to 41), 77.3% (313/405) had had microbiologically proven pTB, and 60.3% (244/403) were HIV-positive. At pTB treatment completion, 60.7% (246/405) reported respiratory symptoms, 34.2% (125/365) had abnormal spirometry, 44.2% (170/385) had bronchiectasis ≥1 lobe and 9.4% (36/385) had ≥1 destroyed lobe on HRCT imaging. At 1 year, 30.7% (113/368) reported respiratory symptoms, 19.3% (59/305) and 14.1% (43/305) of patients had experienced declines in FEV_1 or FVC of ≥100 mL, 16.3% (62/380) had reported ≥1 acute respiratory event and 12.2% (45/368) had symptoms affecting their ability to work.

Conclusions PTLD is a common and under-recognised consequence of pTB that is disabling for patients and associated with adverse outcomes beyond pTB treatment completion. Increased efforts to prevent PTLD and guidelines for management of established disease are urgently needed. Low-cost clinical interventions to improve patient outcomes must be evaluated.

Key messages

What is the key question?

► What is the burden of post-tuberculosis lung damage among adults successfully completing pulmonary tuberculosis (pTB) treatment in urban Malawi, and what are the associated patient outcomes?

What is the bottom line?

► Pulmonary TB-survivors have a high burden of post-TB lung damage, which is largely undiagnosed within existing TB management pathways, and is associated with adverse patient outcomes including accelerated lung function decline, ongoing respiratory-related health seeking, persistent chest symptoms and difficulty working in the year after treatment completion.

Why read on?

► This work provides a detailed description of post-TB lung damage and associated outcomes among both HIV-positive and negative adults successfully completing pTB treatment in Malawi, and suggests research priorities for the prevention and management of disease.

INTRODUCTION

An estimated 10.0 million incident cases of tuberculosis disease occurred globally in 2018, one-quarter of which were in Africa, where 29% of patients are HIV co-infected.[1] TB mortality is falling, and 85% of people treated for a first episode of TB now survive with treatment success (cure or completion).[1]

Post-tuberculosis lung damage (PTLD) is a recognised consequence of pulmonary TB (pTB) disease: adult pTB-survivors have two-to-four-fold higher odds of persistently abnormal spirometry (airway obstruction and restriction) compared with those without previous TB disease,[2–4] with parenchymal and airway abnormalities seen on imaging,[5 6] and associated respiratory symptoms and reduced quality of life.[7–10] However, there are few estimates of the burden of disease at pTB treatment completion, and few prospective data on the medium or long-term consequences of PTLD or risk factors for adverse patient outcomes. Data are particularly scarce for adults in low-income settings with HIV co-infection.[5] There remain no standardised guidelines for the diagnosis and management of PTLD.[11]

Cohort studies from resource-rich settings suggest a correlation between the severity of chronic lung diseases and accelerated spirometry decline, hospital admissions and increased mortality.[12–14] We hypothesise that adults with PTLD in low-income settings could experience similar—or more severe—adverse outcomes.

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To cite: Meghji J, Lesosky M, Joekes E, *et al*. *Thorax* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/thoraxjnl-2019-213808

In this prospective cohort study in Malawi—one of the poorest countries in the world—we investigated the prevalence and pattern of residual lung damage at TB treatment completion using gold-standard respiratory investigations including high-resolution CT (HRCT) imaging and spirometry, with findings disaggregated by HIV-status. The evolution of pathology in the year following treatment completion is described and predictors of adverse outcomes identified.

METHODS

HIV-positive and HIV-negative adults expected to complete treatment for pTB at nine health centres in urban Blantyre, Malawi, between February 2016 and April 2017 were prospectively identified using the Malawi National Treatment Programme (NTP) registry. These individuals were screened by the study team at their monthly medication collection visits, with multiple opportunities available to identify each individual, and formal recruitment was completed at the end of treatment. Inclusion criteria were: age ≥15 years, residence in urban Blantyre, treatment for a first episode of pTB with cure or completion as defined by the NTP. Those with persistent symptoms at treatment completion underwent additional screening with sputum smear and TB culture and were excluded if either were positive. We excluded patients treated as multidrug resistant disease (MDR-TB prevalence among new TB cases in Malawi: 0.75%).[15] All participants provided written informed consent.

Study visits were conducted at the central hospital within 1 month of pTB treatment completion, and at 6 months (home visit) and 12 months (hospital visit) after treatment end. Participants completed: questionnaires (demographics, respiratory exposures, socioeconomic data), the St George's Respiratory Questionnaire (SGRQ); 6-minute walk test; pre-bronchodilator and post-bronchodilator spirometry; blood tests (full blood count, CD4 cell count, Aspergillus IgG). Imaging included chest radiography (CXR) at baseline and 12 months, and non-contrast HRCT chest imaging at baseline. Questionnaires and spirometry were repeated at all visits, and data on health seeking, TB retreatment and all-cause mortality were determined from participant-held health records. Details of existing cardiorespiratory diagnoses were obtained from health records, and TB microbiology at pTB diagnosis from NTP registers.

Questionnaires were conducted in the local language, Chichewa. HIV testing was offered to participants of unknown serostatus, and those who had tested over 1 month before recruitment (Serial testing with Determine 1/2; Alere, USA / Uni-Gold; Recombigen HIV, Trinity Biotech, Ireland). Plasma anti-Aspergillus fumigatus IgG was measured by ELISA (Bordier Affinity Products), using a cut-off index >1.0 for a positive result. Six-minute walk tests and spirometry (EasyOne, ndd Medical Technologies) were conducted to American Thoracic Society standards.[16 17] HRCT imaging was performed using a prespecified protocol (online supplementary appendix 1). Participants underwent protocol-driven clinical review for investigation results requiring urgent intervention but attended routine clinical services for all other illness episodes.

Quality control and data interpretation

Details of spirometry and imaging acquisition, quality control and interpretation are given in the online data supplement. Briefly, only spirometry data meeting the Burden of Obstructive Lung Disease (BOLD) study quality control standards were included in analyses (online supplementary appendix 2). Data were standardised using the Global Lung Initiative 2012 African-American reference ranges.[18] Patterns of abnormality (obstruction: FEV_1/FVC ratio <lower limit of normal (LLN); low FVC: FEV_1/FVC ratio ≥LLN and FVC <LLN; normal: FEV_1/FVC ratio ≥LLN and FVC ≥LLN) and reversibility (>200 mL and >12% increase in absolute FEV_1 or FVC following bronchodilator) were described.[19] HRCT images were independently read by two consultant radiologists with consensus review of discrepant findings (online supplementary appendix 3). The extent and severity of Fleischner-defined airway, parenchymal and pleural pathologies were recorded.[20] Lobes where ≥90% of parenchyma was replaced by banding, atelectasis or cavities/cystic airspaces were classified as 'destroyed'. Agreement between readers was measured using intraclass correlation coefficients and kappa scores.

Statistical methods

A sample size of 400 allowed us to estimate the prevalence of PTLD with a margin of error less than 5% with 95% confidence (online supplementary appendix 4). We described the burden of respiratory pathology using clinical, spirometry and imaging parameters, stratified by HIV-status. X^2, Student's t-test, Fisher's exact or Wilcoxon rank-sum tests were used to compare between groups. We compared the age-stratified prevalence of abnormal spirometry to recent community-based data from urban Blantyre in sensitivity analyses.[21] Exploratory analyses were conducted to determine the relationship between symptoms, and spirometry and imaging parameters.

We determined the proportion of participants experiencing prespecified adverse outcomes over 1 year including: accelerated decline in FEV_1 and FVC (loss ≥100 mL), chronic respiratory symptoms at 1 year (cough, breathlessness, sputum or wheeze ≥few days/month), TB-retreatment and all-cause mortality. We recorded the number of acute respiratory events, defined as 'an unscheduled visit to healthcare provider, either outpatient or inpatient, due to a respiratory complaint (cough, breathlessness, sputum, wheeze, chest pain)'.

We used linear mixed effects and logistic models to estimate predictors of FEV_1 and FVC over time and the prevalence of chronic respiratory symptoms and respiratory events by 1 year. Models were built using a prespecified set of covariates. Fixed effects and variance components were reported for linear mixed effects models, and coefficient estimates or ORs with 95% CIs otherwise. Separate outcome models were constructed using FEV_1 and FVC as predictors, due to colinearity. Complete case analyses were performed in Stata 15 (StataCorp).

RESULTS

Four hundred and fifty pulmonary TB-survivors were screened for eligibility, of whom 405 met inclusion criteria at TB treatment completion (figure 1). 37/405 (9.1%) participants did not complete the final study visit: 22 relocated, 11 died, 3 withdrew and 1 was lost to follow-up. Participants not completing study procedures at 1 year had similar characteristics (age, sex, HIV status, TB microbiology, socioeconomic status, ever smoking/cannabis use) to those completing the study, but a higher prevalence of respiratory symptoms at baseline (75.7% (28/37) vs 59.2% (218/368), p=0.051).

Participant characteristics

Median age was 35 years (IQR: 28 to 41), 67.9% (275/405) were male, and 77.3% (313/405) had microbiologically proven pTB disease (table 1). Among the 60.5% (244/403) who were HIV-positive, the majority were receiving antiretroviral therapy

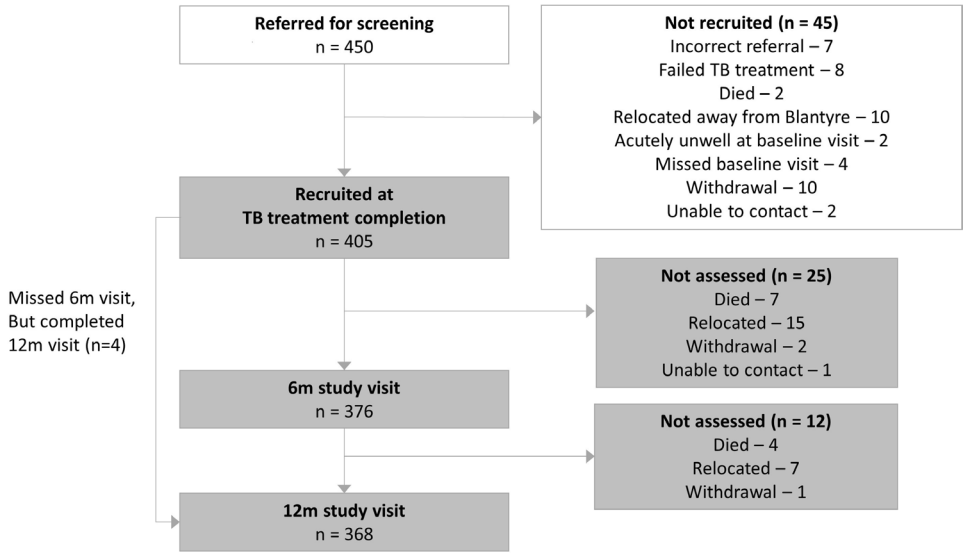

Figure 1 Participant flow diagram.

(ART) (91.8% (224/244)) and cotrimoxazole (90.2% (211/234)), with a median CD4 count of 229 cells/μL (IQR: 127 to 397) and median ART duration of 6.6 months (IQR: 5.5 to 25.6) by TB treatment completion. The median self-reported duration of illness prior to TB treatment initiation was 8.7 weeks (IQR: 4.0 to 13.0).

Socioeconomic deprivation was common: 38.0% (154/405) were educated to primary school level only, 31.6% (128/405) reported intermittent food insecurity and 73.5% (298/405) had incurred dissaving (borrowing money, selling assets or using savings) to cover healthcare costs during TB illness or treatment.

Overall, 29.6% (285/405) of participants had ever-smoked, with a median of 2.7 pack-year (IQR: 0.7 to 6.0) exposure, and 13.3% (54/362) had ever-used cannabis. Use of biomass fuels for cooking/heating was reported by 94.8% (384/405). Only 2.2% (9/405) of the cohort had an established diagnosis of chronic lung disease (bronchitis n=4, asthma n=5) by treatment completion.

Residual lung pathology at TB treatment completion

A majority of participants, 60.7% (246/405, 95% CI: 55.8% to 65.5%), reported one or more respiratory symptom at TB treatment completion (table 2). Median SGRQ total score was 8.8 (IQR: 1.3 to 23.4) and 40.0% (162/405, 95% CI: 35.2% to 45.0%) reported chest symptoms interfering with work. Median oxygen saturation was 98% (IQR: 97% to 99%). Hypoxaemia (<92%) was observed in 1.5% (6/405, 95% CI: 0.5% to 3.2%) at rest, and 3.8% (15/395, 95% CI: 2.1% to 6.2%) after the 6-minute walk test. A total of 17.5% (71/405) of participants were underweight (95% CI: 14.0% to 21.6% (body mass index <18.5 kg/m^2)). Median haemoglobin was 13.7 g/dL (IQR: 12.3 to 15.1). Few participants (0.7% (3/405, 95% CI: 0.1% to 2.1%)) had positive *A.fumigatus* IgG serology (ELISA index >1.0).

BOLD standard post-bronchodilator spirometry data were available for 90.1% (365/405) of participants. Mean z-scores for the FEV_1, FVC and FEV_1/FVC ratio were negative (−1.06 (SD: 1.26), −0.91 (1.23), −0.38 (1.26), respectively). When classified into patterns, 20.0% (73/365, 95% CI: 16.0% to 24.4%) had a low FVC pattern and 14.2% (52/365, 95% CI: 10.8% to 18.3%) had airway obstruction. Among those with airway obstruction 9.6% (5/52, 95% CI: 3.2% to 21.0%) had reversibility. When the age-stratified prevalence of moderate-severe obstruction and low FVC patterns were compared with recent community-based data from urban Blantyre,[21] the prevalence of both obstructive and low FVC patterns were higher in this post-TB cohort across age-strata (online supplementary appendix 5).

The prevalence of cough and exertional breathlessness were higher among HIV-negative compared with HIV-positive participants (45.9% (73/159) vs 29.5% (72/244), p=0.002 and 50.0% (79/158) vs 39.5% (96/243), p=0.038 respectively). Mean FEV_1 and FVC z-scores were also significantly lower among HIV-negative participants (−1.27 (SD: 1.33) vs −0.94 (1.19), p=0.015 and −1.08 (1.29) vs −0.80 (1.18), p=0.037) (online supplementary appendix 6).

In total 385 HRCT scans were completed, with 77.7% (299/385) within 2 months of TB treatment completion. Inter-reader agreement for the extent of Fleischner-defined parenchymal (intraclass correlation coefficient: 0.43 to 0.81) and airway abnormalities (kappa: 0.42 to 0.72) were good to excellent (online supplementary appendix 3).[20] Moderate-to-severe bronchiectasis was seen in ≥1 lobe in 44.2% (170/385, 95% CI: 39.1% to 49.3%) of participants: 7.5% (29/385, 95% CI: 5.1% to 10.6%) had involvement of ≥3 lobes, and 12.7% (49/385, 95% CI: 9.6% to 16.5%) had cystic bronchiectasis. The median amount of abnormal parenchyma was 22.9% (IQR: 9.2% to 39.2%). Atelectasis and banding, and mosaicism were the most common patterns seen, and 9.4% (36/385, 95% CI: 6.6% to 12.7%) of participants had ≥1 destroyed lobe (figure 2). On average, the majority of airways and parenchymal pathologies were significantly more extensive in HIV-negative compared with HIV-positive participants (figure 3, online supplementary appendix 7). However residual consolidation, ground glass opacification and nodules were widespread (prevalence 69.4% (267/385, 95% CI: 64.5% to 73.9%), 36.6% (141/385, 95% CI: 31.8% to 41.7%) and 59.2% (228/385, 95% CI: 54.1% to 64.2%), respectively) with no significant difference by HIV-status.

Participants with weekly or monthly respiratory symptoms at TB treatment completion had lower FEV_1 z-scores (−1.23 (SD: 1.28) vs −0.79 (1.19), p<0.001), lower FVC z-scores (−1.05 (SD: 1.25) vs −0.68 (1.17), p=0.013), more abnormal lung parenchyma (27.3% (95% CI: 10.0% to 42.9%) vs 18.3% (95% CI: 7.1% to 34.6%), p=0.002) and a higher proportion had ≥1 destroyed lung lobe on HRCT imaging (29/234 (12.4%, 95% CI:8.5% to 17.3%) vs 7/151 (4.6%, 95% CI: 1.9% to

Table 1 Participant characteristics, stratified by HIV status*

Characteristic	Total (n=405)	HIV-negative (n=159)	HIV-positive (n=244)	P value
Age (years) (median, IQR)	35 (28–41)	30 (24–37)	37 (32–42)	<0.001
Male sex	275 (67.9%)	115 (72.3%)	158 (64.8%)	0.112
Urban socioeconomic quintile (n=372)*				
Poorest	22 (5.9%)	10 (7.1%)	12 (5.2%)	0.638
Second poorest	85 (22.8%)	28 (19.9%)	57 (24.9%)	
Middle	95 (25.5%)	36 (25.5%)	58 (25.3%)	
Second most wealthy	114 (30.7%)	48 (34.0%)	66 (28.8%)	
Most wealthy	56 (15.1%)	19 (13.5%)	36 (15.7%)	
Maximum education level ≤primary school	154 (38.0%)	49 (30.8%)	104 (42.6%)	0.017
Intermittent difficulty procuring food for household	128 (31.6%)	47 (29.6%)	81 (33.2%)	0.443
Household dissaving incurred in past 1 year to cover illness costs†	298 (73.6%)	109 (68.6%)	189 (77.5%)	0.047
Monthly individual income ($US)‡	41.32 (11.02–96.42)	37.47 (5.51–82.64)	46.83 (16.53–99.17)	0.206
Baseline TB microbiology				
Smear positive	213 (52.6%)	118 (74.2%)	95 (38.9%)	<0.001
Xpert positive, rifampicin sensitive	100 (24.7%)	21 (13.2%)	78 (32.0%)	
Radiological diagnosis	54 (13.3%)	10 (6.3%)	43 (17.6%)	
Clinical diagnosis	38 (9.4%)	10 (6.3%)	28 (11.5%)	
Self-reported illness duration prior to TB treatment (weeks)	8.7 (4.3–13.0)	8.7 (4.3–13.0)	8.7 (4.3–17.4)	0.759
ART use, if HIV-positive (n=244)§			224 (91.8%)	
Duration on ART, if HIV-positive (months) (n=222)			6.6 (5.5–25.6)	
Prophylactic cotrimoxazole use, if HIV-positive (n=234)			211 (90.2%)	
CD4, if HIV-positive (cells/μL) (n=242)			229 (127–397)	
Ever smoker, cigarettes	120 (29.6%)	56 (35.2%)	62 (25.4%)	0.034
Pack years, among smokers (n=120)	2.7 (0.7–6.0)	2.1 (0.7–5.6)	2.9 (0.7–7.0)	0.465
Ever smoker, cannabis (n=362)*	54 (14.9%)	35 (25.4%)	19 (8.6%)	<0.001
Charcoal/wood as main fuel	384 (94.8%)	153 (96.2%)	229 (93.9%)	0.295

*Missing data: HIV status for n=2 (declined to test, included in 'total' column only), socioeconomic status (SES) for n=33 (unable to visit household to determine building materials), Cannabis use for n=43 (unbiased data collection error).
†Borrowing money, using savings, selling assets to cover costs due to illness, in past 1 year (during TB illness and treatment).
‡Income data collected in Malawi Kwacha, but standardised using exchange rate at study midpoint (1 US$: 726 MK, March 2017).
§97% (218/224) receiving Regimen 5a (tenofovir, lamivudine, efavirenz) at TB treatment completion.
ART, antiretroviral therapy.

9.3%), p=0.011) compared to those without regular symptoms. Those with regular cough had higher bronchiectasis severity scores than those without cough (3.0/18 (IQR: 1.0 to 5.5) vs 2.0/18 (0.5 to 4.5), p=0.014) (online supplementary appendix 8).

Change in respiratory health over 1 year

On average, recovery was seen in respiratory health in the year after treatment completion: the prevalence of monthly symptoms declined (60.7% (246/405) to 30.7%(113/368), p<0.001), and average spirometry volumes increased (mean z-score change: FEV_1 +0.20 (95% CI: 0.14 to 0.27) and FVC +0.33 (95% CI: 0.26 to 0.39)). However, by 1 year 12.2% (45/368, 95% CI: 9.1% to 16.0%) still had chest symptoms interfering with work, and mean spirometry z-scores remained negative (FEV_1 −0.88 (SD: 1.19) and FVC −0.61 (SD: 1.09)) (table 2). In addition, 43.2% (159/368, 95% CI: 38.1% to 48.4%) of individuals had experienced a clinically significant deterioration in ≥1 respiratory parameter (symptoms, spirometry or imaging), including 19.3% (59/305, 95% CI: 15.1% to 24.2%) and 14.1% (43/305, 95% CI: 10.4% to 18.5%) of participants with a decline in FEV_1 and FVC ≥100 mL (table 3).

Mixed effects models adjusted for spirometry at TB treatment completion found that FEV_1 and FVC improved by an average of 70 mL (95% CI: 45 to 96 mL) and 131 mL (95% CI: 101 to 161 mL), respectively, over 1 year, with the greatest change seen in the first 6 months (online supplementary appendix 9). However, recovery was incomplete and the strongest predictor of spirometry at any time point was spirometry at TB treatment completion (accounting for >90% of total model variance). Accelerated FEV_1 or FVC decline ≥100 mL was seen in participants across a wide range of baseline FEV_1 and FVC measures (online supplementary appendix 10). The lowest spirometry volumes at 1 year were seen in those with the most extensive parenchymal pathology or bronchiectasis on HRCT, or the presence of symptoms at TB treatment completion.

Chronic respiratory symptoms at 1 year

Respiratory symptoms were reported by 30.7% (113/368, 95% CI: 26.0% to 35.7%) at 1 year, with breathlessness being

Table 2 Clinical and respiratory parameters measured at TB treatment completion, 6-month and 12-month study visits

Parameter	TB treatment completion (n=405)	6-month visit (n=376)	12-month visit (n=368)	P value: Baseline vs 12 months*
Self-reported symptom prevalence (%, 95% CI)†				
Breathlessness				
Never/only with chest infections	227 (56.0%, 51.1% to 60.9%)	283 (75.3%, 70.6% to 79.5%)	282 (76.6%, 72.0% to 80.9%)	<0.001
Few days per month	161 (39.8%, 35.0% to 44.7%)	79 (21.0%, 17.0% to 25.5%)	76 (20.7%, 16.6% to 25.2%)	
≥Several days per week	17 (4.2%, 2.5% to 6.6%)	14 (3.7%, 2.1% to 6.2%)	10 (2.7%, 1.3% to 4.9%)	
Cough				
Never/only with chest infections	259 (64.0%, 59.1% to 68.6%)	284 (75.5%, 70.9% to 79.8%)	307 (83.4%, 79.2% to 87.1%)	<0.001
Few days per month	135 (33.3%, 28.8% to 38.2%)	76 (20.2%, 16.3% to 24.6%)	54 (14.7%, 11.2% to 18.7%)	
≥Several days per week	11 (2.7%, 1.4% to 4.8%)	16 (4.3%, 2.5% to 6.8%)	7 (1.9%, 0.8% to 3.9%)	
Sputum production				
Never/only with chest infections	300 (74.1%, 69.5% to 78.3%)	300 (79.8%, 75.4% to 83.7%)	318 (86.4%, 82.5% to 89.7%)	<0.001
Few days per month	97 (23.9%, 19.9% to 28.4%)	70 (18.6%, 14.8% to 22.9%)	47 (12.8%, 9.5% to 16.6%)	
≥Several days per week	8 (2.0%, 0.9% to 3.9%)	6 (1.6%, 0.6% to 3.4%)	3 (0.8%, 0.2% to 2.4%)	
Wheeze				
Never/only with chest infections	372 (91.8%, 88.7% to 94.3%)	346 (92.0%, 88.8% to 94.6%)	352 (95.7%, 93.0% to 97.5%)	0.091
Few days per month	29 (7.2%, 4.8% to 10.1%)	28 (7.5%, 5.0% to 10.6%)	16 (4.3%, 2.5% to 7.0%)	
≥Several days per week	4 (1.0%, 0.3% to 2.5%)	2 (0.5%, 0.1% to 1.9%)	0	
Any respiratory symptom, ≥monthly	246 (60.7%, 55.8% to 65.5%)	138 (36.7%, 31.8% to 41.8%)	113 (30.7%, 26.0% to 35.7%)	<0.001
Self-reported symptom impact (%, 95% CI)				
Impact of chest on activities				
Does not stop any activities	200 (49.4%, 44.4% to 54.4%)	290 (77.1%, 72.5% to 81.3%)	295 (80.2%, 75.7% to 84.1%)	<0.001
Prevents one to two activities	165 (40.7%, 35.9% to 45.7%)	69 (18.4%, 14.6% to 22.6%)	57 (15.5%, 11.9% to 19.6%)	
Prevents most/all activities	40 (9.9%, 7.2% to 13.2%)	17 (4.5%, 2.7% to 7.1%)	16 (4.3%, 2.5% to 7.0%)	
Impact of chest on work				
Does not affect work	243 (60.0%, 55.0% to 64.8%)	309 (82.2%, 77.9% to 85.9%)	323 (87.8%, 84.0% to 90.9%)	<0.001
Interferes with/made me change work	148 (36.5%, 31.8% to 41.4%)	57 (15.2%, 11.7% to 19.2%)	38 (10.3%, 7.4% to 13.9%)	
Made me stop work	14 (3.5%, 1.9% to 5.7%)	10 (2.7%, 1.3% to 4.8%)	7 (1.9%, 0.8% to 3.9%)	
Breathless at rest/during personal care	2 (0.5%, 0.1% to 1.8%)	2 (0.5%, 0.1% to 1.9%)	2 (0.5%, 0.1% to 1.9%)	1.000
Walks slower than peers/stops for rest at own pace	108 (26.8%, 22.5% to 31.4%)	57 (15.2%, 11.7% to 19.2%)	64 (17.4%, 13.7% to 21.7%)	0.002
Breathless on hills	176 (43.7%, 38.8% to 48.7%)	82 (21.8%, 17.7% to 26.3%)	83 (22.6%, 18.4% to 27.2%)	<0.001
Quality of life				
Self-reported general health (%, 95% CI)				
Poor/fair	115 (28.4%, 24.1% to 33.1%)	54 (14.4%, 11.0% to 18.3%)	22 (6.0%, 3.8% to 8.9%)	<0.001
Good/excellent	290 (71.6%, 66.9% to 75.9%)	322 (85.6%, 81.7% to 89.0%)	346 (94.0%, 91.1% to 96.2%)	
SGRQ total score (median, IQR)	8.8 (1.3–23.4)	0.4 (0–10.6)	0.4 (0–6.9)	<0.001
SGRQ symptom score (median, IQR)	10.3 (2.7–23.1)	2.7 (0–13.7)	2.7 (0–13.7)	<0.001
SGRQ activity score (median, IQR)	11.2 (0–35.5)	0 (0–11.9)	0 (0–6.2)	<0.001
SGRQ impact score (median, IQR)	5.6 (0–15.5)	0 (0–5.7)	0 (0–3.7)	<0.001
Clinical observations				
BMI (kg/m^2) (median, IQR)	20.5 (19.0–22.3)	21.0 (19.4–22.7)	21.1 (19.5–23.2)	<0.001
Oxygen saturations (%) (median, IQR)	98 (97–99)	98 (97–99)	98 (97–98)	<0.001
Hypoxaemia (sats<92%) (%, 95% CI)	6 (1.5%, 0.5% to 3.2%)	6 (1.6%, 0.6% to 3.4%)	4 (1.1%, 0.3% to 2.8%)	0.706
Respiratory rate (breaths/minute) (median, IQR)	18 (17–20)	19 (18–21)	20 (19–22)	<0.001
Heart rate (beats/minute) (median, IQR)	78 (68–89)	77 (68–86)	77 (67–86)	0.019
Pedal oedema (%, 95% CI)	7 (1.7%, 0.7% to 3.5%)	3 (0.8%, 0.2% to 2.3%)	3 (0.8%, 0.2% to 2.4%)	0.317
Palatal Kaposi sarcoma (n=368) (%, 95% CI)	8 (2.2%, 0.9% to 4.2%)	10 (2.7%, 1.3% to 4.8%)	1 (0.3%, 0.0% to 1.5%)	0.008
Blood tests				
Haemoglobin (g/dL) (median, IQR)	13.7 (12.3–15.1)			

Continued

Table 2 Continued

Parameter	TB treatment completion (n=405)	6-month visit (n=376)	12-month visit (n=368)	P value: Baseline vs 12 months*
Positive aspergillus IgG ELISA (%, 95% CI)	3 (0.7%, 0.2% to 2.1%)		2 (0.5%, 0.1% to 1.9%)	0.564
6 minute walk test (n=395/355)				
Distance (m) (mean, SD)	568 m (79.7 m)		611.2 m (71.0 m)	<0.001
Spirometry (n=365/341/336)‡				
FEV_1 z-score (mean, SD)	−1.06 (1.26)	−0.90 (1.25)	−0.88 (1.19)	<0.001
FVC z-score (mean, SD)	−0.91 (1.23)	−0.66 (1.19)	−0.61 (1.09)	<0.001
FEV_1/FVC ratio z-score (mean, SD)	−0.38 (1.26)	−0.51 (1.28)	−0.54 (1.29)	<0.001
Pattern of spirometry (%, 95% CI)				
Obstruction (FEV1/FVC ratio <LLN)	52 (14.2%, 10.8% to 18.3%)	61 (17.9%, 14.0% to 22.4%)	60 (17.9%, 13.9% to 22.4%)	<0.001
Low FVC (FEV1/FVC ratio ≥LLN and FVC <LLN)	73 (20.0%, 16.0% to 24.5%)	45 (13.2%, 9.8% to 17.3%)	43 (12.8%, 9.4% to 16.8%)	
Normal (FEV1/FVC ratio ≥LLN and FVC ≥LLN)	240 (65.8%, 60.6% to 70.6%)	235 (68.9%, 63.7% to 73.8%)	233 (69.4%, 73.5% to 82.6%)	
CXR findings (n=403/361)				
% abnormal parenchyma (median (IQR), (range))	2.9 (0.4–9.2) (0–51.7)		2.1 (0–7.1) (0–70.8)	<0.001
Ring and tramline severity score (0–18) (median (IQR), (range))	1 (0–3) (0–13.5)		1 (0–2.5) (0–14.5)	0.1

*Pairwise comparisons between baseline and 12-month data using McNemar's test for categorical variables, and Student's t-test/Wilcoxon rank-sum for continuous variables.
†Symptom questions derived from SGRQ: Over the past 3 months I have (had shortness of breath / coughed / brought up sputum / had attacks of wheezing): not at all/only with chest infections / a few days a month / several days a week / most days a week; If you have tried to work in the past 3 months: my chest trouble does not affect my work / my chest trouble interferes with my work or made me change my work / my chest trouble made me stop work; Which of these statements best describes how your chest affects you: It does not stop me doing anything I would like to do / it stops me doing one to two things I would like to do / it stops me doing most of the things I would like to do / it stops me doing everything I would like to do.
‡BOLD standard data available for n=365/405 at baseline, n=341/376 at 6 months, and n=336/368 at 12 month study visits. Data age / sex / height standardised using GLI 2012 African-American reference ranges to generate z-scores.
BMI, body mass index; CXR, chest radiography; GLI-2012, Global Lung Initiative 2012; LLN, lower limit of normal; SGRQ, St George's Respiratory Questionnaire.

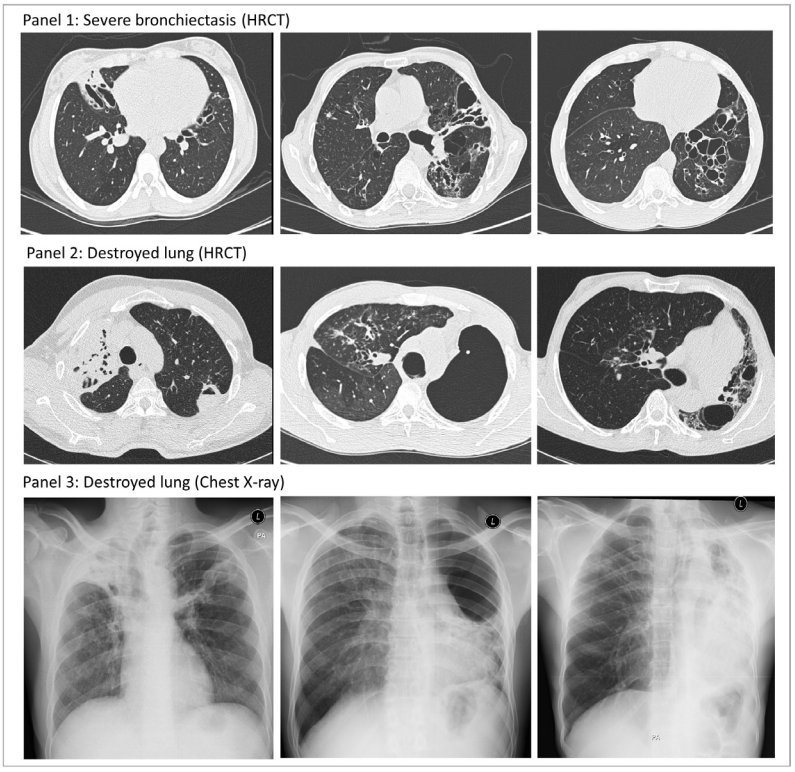

Figure 2 High resolution CT (HRCT) and chest x-ray imaging from participants with severe bronchiectasis (panel 1) or destroyed lung (panels 2 and 3, paired imaging from the same individuals), captured at TB-treatment completion. Bronchiectasis: Airway lumen diameter greater than accompanying pulmonary artery outer diameter, or airways visible <1 cm of lung periphery, or lack of normal airway tapering. Destroyed lung: ≥1 lung lobe in which ≥90% of parenchyma occupied by atelectasis or parenchymal banding, or destroyed by cavities/cystic airspaces.

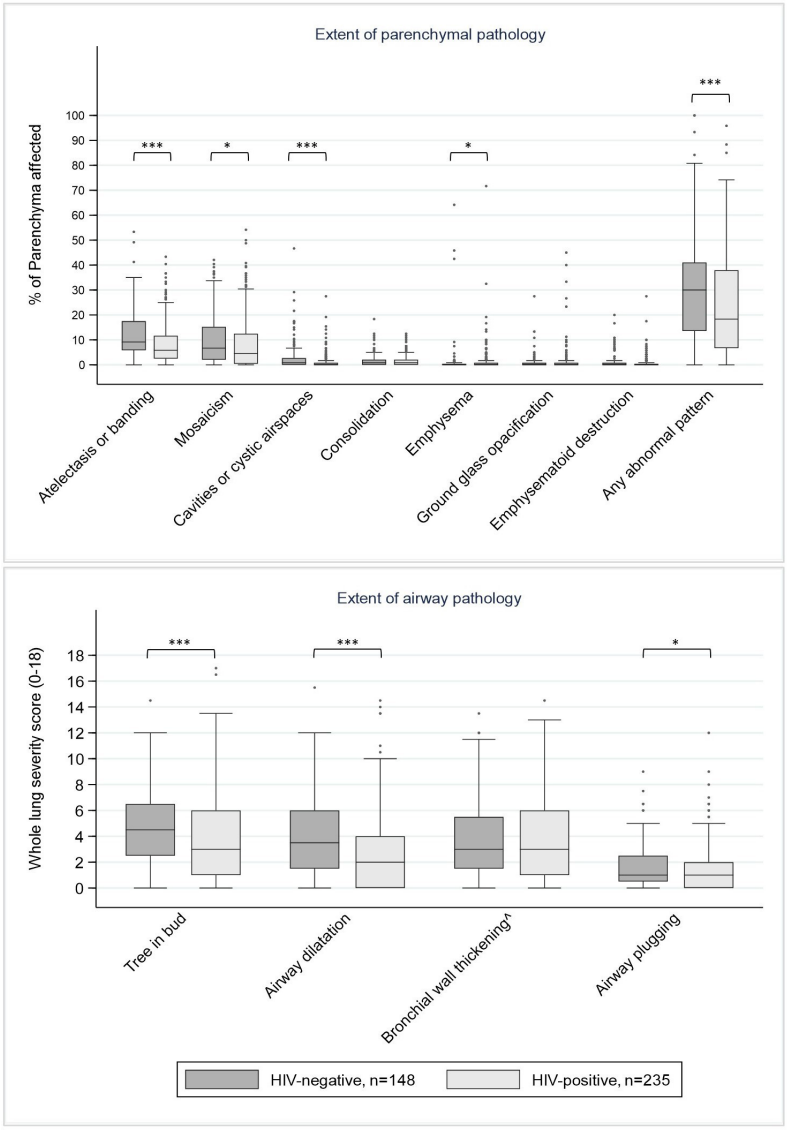

Figure 3 The extent of parenchymal and airway pathology seen on high-resolution CT imaging at TB treatment completion, stratified by HIV status (n=385). HRCT data missing for n=25: pregnancy (n=3), unable to travel to CT-scanner (n=6), missed appointments (n=8) and machine errors (n=3). ^ Bronchial wall thickening: Not reported for those with lobar destruction preventing evaluation of bronchial wall thickness in ≥1 lung lobe (n=58). *p<0.05, **p<0.01, ***p<0.001.

most common (table 2). On average, participants reporting respiratory symptoms at pTB treatment completion were significantly more likely to have symptoms 1 year later compared with those without baseline symptoms (OR 2.42 (95% CI: 1.37 to 4.27) and 2.45 (95% CI: 1.39 to 4.32) in models controlling for either baseline FEV_1 or FVC). The odds of respiratory symptoms at 1 year were lower in HIV-positive compared with HIV-negative participants (OR 0.33 to 0.40 (95% CI: 0.18 to 0.98) across CD4 groups and models) (online supplementary appendix 11).

Acute respiratory events over 1 year

Of participants who contributed 6 and 12 months of follow-up data, 25.0% (4/16, 95% CI: 7.3% to 52.4%) and 15.9% (58/364, 95% CI: 12.3% to 20.1%) experienced ≥1 acute respiratory event. The majority had one episode (77.4% (48/62)). Of the 70 unscheduled outpatient visits to local health centres or hospitals, 55.7% (39/70, 95% CI: 43.3% to 67.6%) were due to increased cough and 34.3% (24/70, 95% CI: 23.3% to 46.6%) were related to increased breathlessness. Antibiotics were prescribed in 80% of cases.

Participants with respiratory symptoms at treatment completion were more likely to report a respiratory event during follow-up (OR 2.6 (95% CI: 1.25 to 5.42)) compared with those without baseline symptoms. HIV-positive adults (12.9% (30/232, 95% CI: 8.9% to 17.9%)) had lower odds of a respiratory event compared with HIV-negative participants (21.9% (32/146, 95% CI: 15.5% to 29.5%)) in all models and at CD4 counts above and below 200 cells/µL (OR 0.33 to 0.43 (95% CI: 0.13 to 0.90)) (online supplementary appendix 12).

Controlling for baseline lung pathology the presence of more than one respiratory event during follow-up was negatively correlated with FEV_1 and FVC volumes at 1 year. On average, those with ≥1 acute respiratory event had FEV_1 and FVC volumes which were 82 mL (95% CI: 17 to 147 mL) and 122 mL (95% CI: 51 to 192 mL) lower at 1 year compared with those without events (online supplementary appendix 13).

Table 3 Proportion of participants experiencing clinically relevant improvement, deterioration or no change in respiratory parameters between baseline and 1 year study visits, among those completing both visits (n=368), with median size of change shown for continuous variables.

		Proportion of participants with each pattern of change (n, %)* Median (IQR) change observed		
Parameter	**Classification of change**	**Improvement**	**No change**	**Deterioration**
Self-reported general health	Change of ≥1 category in self-reported general health (poor, fair, good, excellent)	115 (31.3%)	229 (62.2%)	24 (6.5%)
BMI (kg/m^2)	Change ≥1.46 kg/m2†	105 (28.5%) 2.7 (1.9 to 4.1)	244 (66.3%) 0.2 kg/m^2 (–0.2 to 0.8)	19 (5.2%) –2.4 kg/m^2 (–3.4 to –1.7)
SGRQ total score (n=366)	Change ≥4units‡	167 (45.6%) –16.1 points (–23.8 to –9.2)	153 (41.8%) –0.4 points (–1.8 to 0)	46 (12.6%) +11.5 points (7.0 to 25.9)
6 min walking distance (m) (n=348)	Change ≥26 m‡	201 (57.8%) 70 m (46 to 105 m)	102 (29.3%) 8 m (–4 to 15 m)	45 (12.9%) –49 m (–65 to –38 m)
Presence of monthly respiratory symptoms	Change between present / absent monthly symptoms	133 (36.1%)	207 (56.3%)	28 (7.6%)
FEV1 volume (L) (n=305)	Change ≥100 mL‡	133 (43.6%) 230 m (150 to 340)	113 (37.1%) 0 mL (–40 to 40)	59 (19.3%) –200 mL (–230 to –130)
FVC volume (L) (n=305)	Change ≥100 mL‡	164 (53.8%) 280 mL (190 to 400)	98 (32.1%) 30 mL (–40 to 60)	43 (14.1%) –160 mL (–220 to –120)
% abnormal parenchyma on CXR (n=359)	Change ≥4.68%†	58 (16.2%) –8.3% (–12.1 to –6.3)	283 (78.8%) 0% (–1.7 to 0.4)	18 (5.0%) +7.9% (6.3 to 13.3)
Ring and tramline score (0–18) on CXR (n=359)	Change ≥1.17 points†	79 (22.0%) –2.5 points (–4.0 to 2.0)	218 (60.7%) 0 points (–0.5 to 0)	62 (17.3%) 2.0 points (1.5 to 3.0)

*Pattern of change over 1 year period, classified using 'Minimally important clinical difference (MCID)' cut-offs for continuous variables, and change in response category for ordinal variables. Improvement: Increase ≥MCID or improvement by ≥1 category; No change: Remaining within +/-MCID of baseline reading, or remaining in same category; Deterioration: Reduction ≥MCID or deterioration by ≥1 category.
†No existing MCID agreed in literature: cut-off calculated by 0.5 x SD of baseline data.
‡MCID derived from COPD literature.[42]
BMI, body mass index; CXR, chest radiography; SGRQ, St George's Respiratory Questionnaire.

TB retreatment and mortality over 1 year

The TB symptom screen (≥1 of current cough, fevers, night sweats, weight loss, haemoptysis) was positive in 18.9% (71/376, 95% CI: 15.1% to 23.2%) and 10.6% (39/368, 95% CI: 7.6% to 14.2%) at the 6-month and 12-month visits, with current cough as the most common symptom reported (95.8% (68/71, 95% CI: 88.1% to 99.1%) and 92.3% (36/39, 95% CI: 79.1% to 98.4%) at 6 and 12 months). Sputum was obtained at 100/110 of these visits, and only 4% (4/100) had *Mycobacterium tuberculosis* (MTB) on culture. Three non-tuberculous mycobacteria isolates were cultured but repeat samples were negative. TB-retreatment was initiated in 3.7% (15/404) of participants during follow-up: two culture positive, five smear positive, four Xpert MTB/RIF positive, three radiological diagnosis, one unknown. 2.7% (11/404) of participants died, of whom 45.5% (5/11) had been initiated on TB retreatment and 90.9% (10/11) were HIV-positive.

DISCUSSION

This study used gold-standard measurement approaches to show that among a prospectively recruited, unselected cohort of pTB-survivors in a low income, high TB and HIV prevalence setting, the burden of PTLD is high: after a single episode of successfully treated pTB disease, one-third of patients have abnormal spirometry, over 40% have bronchiectasis and almost 10% have lobar destruction. This pathology is largely undiagnosed within existing TB management pathways, but is meaningful for patient outcomes, with accelerated lung function decline, ongoing respiratory-related health seeking, persistent chest symptoms and symptoms impairing work seen in 12% to 31% of patients in the year after treatment completion. Patterns of PTLD were heterogeneous, and although less severe among HIV-positive compared with HIV-negative patients, the burden of disease was marked in both groups.

The finding of a high burden of post-TB lung damage is consistent with previous literature which suggests two-to-four-fold increased odds of airway obstruction and restriction among those who have previously had pTB disease compared with those who have not,[2–4] and ongoing airway and parenchymal imaging abnormalities following treatment success.[5 6] Together, these data indicate a high population burden of respiratory pathology resulting from pTB disease.

To our knowledge, this is the first study to track change in lung function in an unselected patient cohort prospectively from pTB treatment completion. On average, FEV_1 and FVC values for the cohort improved over time. Recovery was incomplete, but most marked in the first 6 months. This pattern of partial recovery is consistent with previous models,[22] and is in keeping with the parenchymal destruction and airway dilatation seen on HRCT imaging which are unlikely to fully resolve.[23 24] However, heterogeneity of lung function outcomes was observed between individuals within the cohort: while most experienced recovery, up to a fifth had a clinically meaningful decline in lung function over time. These patients are of particular concern given the known associations between reduced FEV_1 and FVC, and increased mortality.[25–27] In keeping with data from other chronic lung diseases, our analyses suggest that acute respiratory events in the year following treatment completion may drive worsening spirometry.[12 13]

Our data show that PTLD is relevant to patients' lives and livelihoods. Chest symptoms interfering with work were reported by 46% at pTB treatment completion and 12% 1 year later. The high costs incurred by TB patients during diagnosis and disease treatment

are well recognised and have been associated with adverse treatment outcomes.[28 29] However, our findings suggest that post-TB morbidity may cause ongoing income losses even beyond treatment completion. These ongoing costs are not routinely included in calculations of the economic impact of TB disease, nor is the need to address them yet prioritised within the WHO 'End-TB' agenda, which aims to mitigate TB-related patient costs.[30]

Almost one-third of patients reported ongoing respiratory symptoms at 1 year. Chronic cough is stigmatising in high TB and HIV burden settings,[31] and in this study also led to the WHO TB-symptom screening tool remaining positive for many patients, some months after their initial disease episode. Although pTB-survivors are at high risk of recurrent TB disease,[32] empirical TB retreatment of pTB-survivors based on chronic symptoms is also widespread.[33] In this study the majority of those reporting chronic cough during follow-up did not have microbiological evidence of pTB when retested, were not started on TB retreatment, and did not die, highlighting challenges with TB diagnosis in the post-TB population.

HIV-positive adults had less extensive PTLD compared with HIV-negative adults, despite similar self-reported illness duration prior to TB treatment initiation. HIV-TB co-infected adults with low CD4 counts have been shown to have less extensive CXR changes at TB diagnosis, due to impaired localised cellular immune responses to mycobacterial infection, and our data suggest that this translates into less extensive residual pathology at TB treatment completion.[34 35] However, it is of note that although the burden of disease was lower among HIV-positive compared with HIV-negative adults, still moderate-to-severe bronchiectasis or abnormal spirometry was seen in a third of this group at pTB treatment completion. Most HIV-infected participants in this cohort were initiated on ART close to pTB treatment onset, with median CD4 count of only 229 cells/μL at TB treatment completion. Immune reconstitution on ART has been associated with lung inflammation and destruction during early treatment.[36 37] Findings in this study may reflect a balance between the protective effect of low CD4 counts at TB diagnosis, and pro-inflammatory immune reconstitution with early initiation of ART.

Lastly, the heterogeneity of patterns of PTLD in this study was marked. Novel HRCT imaging findings included a high burden of mosaicism - this may reflect small airways disease but may also relate to pulmonary vascular disease, and echocardiography in this cohort would be of value.[38] The high prevalence of consolidation, ground-glass and nodules even after 6 months of TB treatment was striking, but consistent with positron emission tomography-CT studies from South Africa which show ongoing metabolic activity in focal lung lesions of pTB-survivors, due either to persistent mycobacterial disease or a protracted host immune response to sterilised infection.[39] The long-term relevance of this residual inflammation is not yet clear.

This is one of the first studies to prospectively investigate the nature and outcomes of post-TB lung damage, from the point of TB treatment completion, in a resource-poor setting in sub-Saharan Africa. The broad eligibility criteria mean that findings can likely be generalised to a wide spectrum of adults completing treatment in similar settings. Multiple respiratory parameters were measured to comprehensively describe pathology, with high standards of quality control and best-practice reporting, and outcome data were collected prospectively. The availability of CT imaging is limited in low- and middle-income countries, and its inclusion is therefore of particular value. Although the study was completed within an urban setting with a highly mobile population, loss to follow-up was under 10%.

As patients were not assessed prior to TB disease and no control group was included for comparison, the aetiology of lung pathology cannot be confirmed. The short follow-up duration of 1 year means that models of patient outcomes may have been underpowered and precluded investigation of risk factors for TB retreatment or mortality. Observed changes over time may be related to regression to the mean, test-retest variation or participant learning, but minimally important clinical difference cut-offs were used to allow for this. Study recruitment required attendance at a central hospital, and a selection bias away from those with severe disease may exist. Although this study was observational, participants likely received more medical advice than routinely available, and findings may be biased towards improved outcomes.

In summary, this study has found that PTLD is a common and under-recognised consequence of pTB that is disabling for patients and associated with adverse outcomes beyond pTB treatment completion. Our data highlight the importance of preventing PTLD: further investigation of host, environment and pathogen determinants of the nature and severity of PTLD, including HIV-specific factors, are required to identify upstream modifiable risk factors.[40] Host directed therapies, and earlier TB diagnosis through active case finding and improved diagnostics may reduce lung damage, and we suggest that the burden of PTLD should be included as a secondary outcome in studies investigating the impact of these approaches.

Evidence-based guidelines for the management of those with established PTLD are lacking but urgently needed.[11] It is not yet clear which interventions would be clinically and cost-effective at maximising health and preventing ongoing decline after pTB treatment completion, but our data suggest that appropriate management of respiratory exacerbations, and improved screening pathways for recurrent pTB disease should be prioritised. Other low-cost strategies including pulmonary rehabilitation and airway clearance exercises require evaluation, and health systems capable of providing long-term care to pTB-survivors will be needed to deliver these services.[41] Ultimately, we suggest that renewed efforts by the global TB research and practice community to address the sequelae of TB disease, beyond treatment completion, will be required to improve long-term patient well-being.

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Acknowledgements We are grateful for the support of the Malawi National Treatment Programme and TB Officers, and the patients who participated in this study. We thank Lindsay Zurba for her role in spirometry training and quality control, Bayu Wilopo for performing the aspergillus serology and the study team (Beatrice Chinoko, Malumbo Ng'oma, Hygiene Kumwenda, Rabecca Kondowe) for their work in data collection.

Contributors JM, SBS and KM were responsible for study conceptualisation and design. JM performed data collection. JM, PB and JR provided clinical oversight of the cohort. SBG, ELC and SBS provided institutional support in Malawi. JM, EJ, JJ and HZ developed image reporting systems and performed image reading. JM, ML, PM

and KM analysed and interpreted data. JM was the lead author, with input from all co-authors. JM had final responsibility for the decision to submit for publication.

Funding Funded by a Wellcome Trust PhD Training Fellowship to JM (106065/Z/14/A). Additional support from The Wellcome Trust (Clinical Career Development Fellowship to PM (206575/Z/17/Z), Clinical Career Development Fellowship to JJ (209553/Z/17/Z), Senior Research Fellowship to ELC (200901/Z/16/Z), Malawi-Liverpool-Wellcome Trust Core Award to SG (206545/Z/17/Z)), an EDCTP2 Senior Fellowship (TMA2017SF-1959) and Academy of Medical Sciences Newton Advanced Fellowship (NAF\R2\180681) to ML and support to ML, BS and KM from the NIHR Global Health Research Unit on Lung Health and TB in Africa at the Liverpool School of Tropical Medicine (16/136/35). The funders had no role in study design, data analysis and interpretation or writing of this manuscript.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Ethical approval was obtained from the Liverpool School of Tropical Medicine (15.040RS) and Malawi College of Medicine Research Ethics (P.10/15/1813) Committees.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Individual deidentified participant data that underlie the results reported in this article will be available, together with the study protocol, beginning 12 months after article publication. Data will be made available by the corresponding author to researchers with a methodologically sound protocol, and independent review committee approval for data use, upon reasonable request.

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Supplementary Materials

Manuscript title:

Patient outcomes associated with post-tuberculosis lung damage in Malawi: a prospective cohort study

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Meghji J, *et al. Thorax* 2020;0:1–10. doi: 10.1136/thoraxjnl-2019-213808

Appendix 1: CT scanning protocol

All participants were offered low-dose HRCT imaging at pTB treatment completion, except for those with contraindications: absence of informed consent, positive pregnancy test / self-reported current pregnancy, inability to travel to the imaging centre. Those with positive TB symptom screens (cough, weight loss, fever, night sweats, haemoptysis) at pTB-treatment completion were asked to submit sputum, and only booked for imaging if smear negative.

For logistical reasons, 2 imaging centres were used: Blantyre Adventist Hospital (BAH), Blantyre (Feb – Aug 2016) and Kamuzu Central Hospital (KCH), Lilongwe (Nov 2016 – May 2017). The same unenhanced low dose imaging protocol was used at both sites (Table E1). Imaging was performed supine in full inspiration, with coverage from apices to bases. Scans were reconstructed using a lung algorithm only, accepting that this would give limited diagnostic quality for soft tissue. Images were stored in DICOM format electronic files.

Table E1: Non contrast high resolution CT scanning protocol

Topogram

mA	kV	Scan time	Slice	Topogram length	Tube position	Direction	API	Kernel	Window	Tilt
50	120	5.3 sec	1.0 mm	512 mm	Top	Cranio-caudal (Supine)	Inspiration	T20s Standard	Topogram body	0.0°

Scan

Effective mAs	kV	Scan time	Delay	Slice	CTDL Vol	Pitch	Acquisition	Care dose
50 depending on patient size	120 depending on patient size	12.05	5 sec	Volume HRCT 1mm at 1mm intervals	3.90 mGy	1.15	Spiral scan	Care Dose 4D

Processing

Reconstuction	Image order	Reconstruction increment	Kernel	Window	Field of view	Centre X	Centre Y	3D
Axial	Cranial-caudal	1.0mm	B60f	Lung window	380	0 mm	0 mm	VRT & MIP as needed

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Appendix 2: Spirometry quality control procedures

Spirometry measurement

Pre- and post-bronchodilator spirometry were performed at each study visit – each participant performed up to eight attempts for each, until three high quality curves were obtained. Where consistently poor technique / difficulty performing the test was observed, participants were asked to return on another occasion for repeat testing. Salbutamol was administered via a spacer after the pre-bronchodilator tests, using two 100mcg doses from an MDI device. A minimum of 15 minutes was allowed between administration of salbutamol and repeat spirometry. Nose clips were found to function poorly in the study population, so participants were asked to pinch their noses during testing. Disposable spirettes were used and changed for each patient. Testing was performed in the seated position during baseline and 12-month visits, and at the 6-month visit if suitable seating was available. Participant age (years), standing height (mm), and weight (kg) were recorded contemporaneously for standardization of results. Spirometry data were stored electronically using EasyWare software.

Spirometry quality control

All pre- and post- spirometry attempts were reviewed by two readers (JM & LZ) independently, and graded for errors according to the CDC National Institute for Occupational Safety & Health (NIOSH) guidelines, and the BOLD study quality control procedures (Table 2).(1, 2) Tests were reviewed in chronological order in batches of 100, and grading was resolved by consensus discussion in the event of discrepancy. The 5% of usable spirometry readings with the longest Forced Expiratory Times (FET) values, and readings with the 1% highest and lowest FEV_1 and FVC values were manually reviewed, and patient results compared across study visits to ensure consistency and accuracy. Curves which

were clearly inconsistent with other data for a given patient, where a zero-flow error was suspected, or where there was suspicion of an error in study ID or test performance, were classified as invalid.

Table E2: Grading criteria for individual spirometry trials, with source of guidelines listed

Reason for rejection of spirometry curve	Abbreviation for error	Definition of error	Reference/ source
High PEFT	p (PEFT)	PEFT ≥150msecs	BOLD QC requirements, which relaxed the ndd cut off of 120ms
High BEV	b (BEV)	BEV ≥150ml AND BEV ≥5% of FVC	ATS criteria, NIOSH, BOLD QC requirements state that for a curve to be included BEV must be <5% or <150ml, whichever is greater.
Non-maximal effort	e (effort)	Marked lack of peak, indicating weak blast OR Markedly reduced peak compared to other curves, indicating poor filling of lungs at start of test	BOLD QC requirements ATS criteria NIOSH guidelines
Early termination of expiration	t (termination)	Insufficient expiratory phase on volume-time curve – duration of expiration for < 6 secs OR failure to reach plateau of ≥1 sec OR Sharp early drop to 0 on flow-volume curve	BOLD QC requirements ATS criteria NIOSH guidelines
Extra breath	x (extra)	Visible extra breath on flow-volume and or the volume-time curves	BOLD QC requirements NIOSH guidelines
Glottis closure that influences measurement	g (glottis)	Abrupt flat line on volume-time curve, with sharp drop to 0 on flow-volume curve	BOLD QC requirements ATS criteria NIOSH guidelines
Leak	l (leak)	Descent of volume-time curve, after peak is reached, with 'back-track' of flow-volume curve at the end of expiration	BOLD QC requirements ATS criteria NIOSH guidelines
Obstructed mouthpiece	o (obstruction)	Artefact in the flow-volume and volume-time curves, felt to be significant enough to affect measurement	BOLD QC requirements ATS criteria NIOSH guidelines
Cough that affects measurement	c (cough)	Cough within 1st second which is likely to alter FEV_1, or a later cough which causes early termination.	BOLD QC requirements ATS criteria NIOSH guidelines
Zero flow error	z (zero)	Continuous rise of volume-time curve, with no plateau, and long tail on flow-volume curve, which is felt related to error rather than obstructive impairment	BOLD QC requirements NIOSH guidelines

PEFT: Peak expiratory flow time; BEV: Back extrapolated volume; BOLD: Burden of Obstructive Lung Disease Study; ATS: American Thoracic Society; NIOSH: National Institute for Occupational Safety & Health, Centres for Disease Control & Prevention; QC: Quality Control.

Data were used for a given patient at a given study visit only if 2 usable curves with no errors were available, and if the differences between both the best/next-best FEV_1 and FVC readings between these curves was ≤200ml. Patients with spirometry which did not meet these criteria were defined as having 'missing' data for this study visit.

Spirometry interpretation

Spirometry data meeting these standards were standardised for age, sex and height using the Global Lung Initiative 2012 (GLI-2012) African reference ranges.(3) Data were described using z-scores, and 5% lower limit of normal (LLN) cut-offs used to determine patterns of abnormality (obstruction: FEV_1/FVC ratio <LLN; low FVC: FEV_1/FVC ratio ≥LLN & FVC<LLN; normal: FEV_1/FVC ratio ≥LLN & FVC≥LLN). Reversibility was defined as a >200ml and >12% increase in absolute FEV_1 or FVC following bronchodilator.(4)

Appendix 3: HRCT reporting procedures

Derivation of scoring tool

There exist no validated image scoring tools for the measurement of post-TB lung damage. A novel tool was therefore developed for use here (Table 3). This was informed by a systematic review of the existing literature on post-TB lung damage,(5) pictorial essays of chest imaging at various stages of PTB disease, and review of image scoring systems commonly used in bronchiectasis, COPD, and interstitial lung disease studies. It was developed by the study PI (JM) and two consultant radiologists: a consultant chest radiologist with predominantly UK specialist respiratory experience (JJ), and a UK-based ID radiologist with experience of TB related pathology and imaging in sSA (EJ). Particular attention was paid to the selection of variables used to measure bronchiectasis and airways pathology. Established radiological criteria from the Fleischner guidelines were used throughout,(6) except for the category of 'Emphysematoid destruction' which is a feature described in the TB and interstitial lung disease (ILD) literature only.(7) Joint scoring of a training set of CT images obtained from a previous study of patients receiving TB-retreatment in urban Blantyre was used to refine the scoring tool prior to use.

Image scoring

All HRCT images were independently scored by two consultant radiologists (EJ and JJ). Anonymised images were used, with no accompanying demographic or health related information, and images were provided to both radiologists in the same format and order over the course of the study. CTs were scored on a lobar basis. For scoring purposes the lingula was counted as a separate lobe using the level of the origin of the lingula bronchus to demarcate the boundary of the lingula from the left upper lobe. Scores were entered directly into a live reporting database.

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Data from the first 20 independently reported scans from within this study were openly reviewed by both primary readers together to consolidate training. Re-scoring of initial data for these first 20 scans was permitted following this review, but all subsequent images were independently reported with no comparison or changes allowed.

Table E3: Novel HRCT chest scoring tool, for post-tuberculosis lung damage

Variable	Definition	Lobar level scoring options
PARENCHYMAL VARIABLES	Scored at lobal level. Percentage of parenchyma affected by each pattern estimated to nearest 5%. Lobar percentages summed over whole lung to give total lung score /600.	
Parenchymal bands	Linear opacity 1-3mm thick, up to 5cm long. Usually extends to visceral pleura. May be accompanied by anatomical distortion	% of parenchyma (to nearest 5%)
Atelectasis	Reduced lung volume which may be accompanied by displacement of fissures, bronchi, vessels.	
Consolidation	Homogeneous increase in lung parenchymal attenuation which obscures the margins of vessels and airway walls. An air bronchogram may be present.	
Ground glass opacification	Hazy increased lung opacity with preservation of bronchial and vascular margins	
Mosaicism	Specifically, the low attenuation component of a variable “mosaic” attenuation pattern within the lung	
Emphysema	Focal areas or regions of low attenuation usually without visible walls	
Emphysematoid destruction	Focal area of destruction/emphysematous change associated with features of healing TB, suggesting destruction of acini/small airways.	
Cavities / cystic airspaces	Gas filled structure, seen as a lucency or low-attenuation area within a pulmonary consolidation, a mass, or a nodule. Consolidation may have resolved leaving a thin wall only.	
Normal	Normal parenchyma, not affected by any of the pathological processes above	
BRONCHIECTASIS VARIABLES	Scored at lobar level. Lobar extent and severity scores summed across whole lung to give total score /18.	
Bronchiectasis Airway lumen diameter greater than accompanying pulmonary artery outer diameter, OR Airways visible within 1 cm of the lung periphery, OR Lack of normal airway tapering	Extent (Maximal score of 2 for middle lobes – 2 segments only)	0: Absent 1: ≤1 BP segment 2: 2 BP segments 3: ≥ 3 BP segments
	Pattern (Nominal variable, scored only if bronchiectasis seen and ‘extent’ score >0)	1: Cystic (‘Ballooned' outline, with diameter increasing towards periphery) 2: Cylindrical (Regular and straight outline, with abrupt termination) 3: Varicose (Irregular beaded bronchial outline with bulbous termination)
	Severity Maximum degree of airway dilatation, to be measured by comparing diameter of airway lumen to diameter of adjacent vessel. (Scored only if bronchiectasis seen and ‘extent’ score >0)	1: Trivial (bronchial lumen is <twice adjacent vessel diameter) 2: Bronchial lumen is 2-3 times adjacent vessel diameter 3: Bronchial lumen is >3 times adjacent vessel diameter
AIRWAY VARIABLES	Scored at lobar level. All variables independent of each other. Lobar scores summed across whole lung to give total score /18.	

Bronchial wall thickening	Thickening of bronchial walls	0: Absent 1: Mild 2: Moderate 3: Severe Missing: Unable to assess
Airway plugging	Plugging seen in large airways	0: Absent 1: Mild 2: Moderate 3: Severe
Tree in bud	Centrilobular branching pattern in the peripheral airways, resembling a budding tree.	0: Absent 1: Mild 2: Moderate 3: Severe
CAVITY VARIABLES	Scored at lobar level. Independent of parenchymal scores. Lobar scores combined to give whole-lung data.	
Cavity / cystic airspace Gas filled space, seen as a lucency or low-attenuation area within a pulmonary consolidation, a mass, or a nodule. Consolidation may have resolved leaving a thin wall only.	Extent	0: Absent 1: 1-2 cavities 2: 3-5 cavities 3: >5cavities
	Maximum size (Scored only if bronchiectasis seen and 'extent' score >0)	Maximum diameter (mm)
	Mycetoma Discrete mass of hyphae, within a cavity. May have air crescent sign. May have sponge like pattern with areas of calcification. (Scored only if bronchiectasis seen and 'extent' score >0)	0: Absent 1: Present
OTHER LOBAR VARIABLES	Scored at lobar level, with scores combined to give whole-lung data	
Nodules	Rounded opacities, well or poorly-defined, >5mm, measuring up to 3cm in diameter	0: Absent 1: <5 nodules 2: ≥5 nodules 3: Miliary
WHOLE LUNG VARIABLES	Scored at level of hemithorax / whole lung	
Pleural effusion	Accumulation of fluid within pleural space	0: Absent 1: Present
Pleural thickening	Pleural thickening of ≥10mm	0: Absent 1: Present
Lymph nodes	Mediastinal / hilar lymph nodes ≥10mm diameter	0: Absent 1: Present

Lobar scores generated for each variable were summed across the whole lung, and these whole lung scores were then compared between readers. The Cohen's kappa score (binary variables), weighted Cohen's kappa score with quadratic weighting (ordinal variables with multiple categories), and intra-class correlation coefficients (continuous variables) were calculated to measure inter-reader agreement.

Consensus review of imaging reports

Consensus review was completed for the scans with the most discrepant scores for reported variables (Table 5), with cut-offs specified after review of the primary reporting data. For continuous variables, the most discrepant ~5% of scans for each variable were selected for review: assuming that the difference in scores between readers had a normal distribution, this rule identified scans with differences >2 standard deviations away from the mean difference for each variable, but allowed the absolute magnitude of discrepancy tolerated to vary between variables. Where a variable required review for a particular scan, all lobes in which discrepancy was seen between original readers were reviewed by the consensus reader.

Consensus reading was performed by a third independent chest radiologist (HZ). Reviews were performed at the end of the study, and the consensus reader was provided with both the HRCT images and anonymised original reads from each of the primary radiologists. When reviewing discrepant variables/lobes, the reviewer was able to either choose one of the original scores or generate their own response. For pragmatic reasons, no consensus review was performed for pleural pathology (final readings were taken from one reader only) and lymphadenopathy for which non-contrast imaging is known to have limited sensitivity and which was shown to have very low inter-reader agreement suggesting poor validity of data.

Table E4: Methods used to select scans and variables for consensus review, including the difference in scores used as a cut-off for consensus reading, the number of scans reviewed and the approach underlying this decision given.

Variable group	Variable (Range of possible scores, whole lung level)	Inter-reader consistency for whole-lung variable ICC (95% CI) OR Kappa (SE)	Threshold difference, at which consensus review required	Number of scans for review of ≥1 lobe	Number of lobes for which clean reads available (RUL/RML/RLL – LUL/Lingula/LLL) n (%) of scans with all lobes having clean reads[††]
Parenchymal variables	Atelectasis score (0-600)	ICC: 0.81 (0.77-0.84)	≥60 points	20	R lobes: 308 / 330 / 334 L lobes: 308 / 321 / 332 Clean reads all lobes: 177/385 (46.0%)
	Parenchymal banding score (0-600)	ICC: 0.43 (0.35 -0.51)	≥75 points	22	R: 221/204/232 L: 231 / 244/ 238

					Clean reads all lobes: 86/385 (22.3%)
	Consolidation score (0-600)	ICC: 0.43 (0.34 – 0.51)	≥40 points	18	R 311 / 346 / 338 L: 301 / 338 / 342 Clean reads all lobes: 194/385 (50.4%)
	Ground glass opacification score (0-600)	ICC: 0.49 (0.41 – 0.57)	≥60 points	22	R: 353 / 367 / 366 L: 362/366 / 360 Clean reads all lobes: 292/385 (75.8%)
	Mosaicism score (0-600)	ICC: 0.55 (0.48-0.62)	≥160 points	22	R: 236 / 242/232 L: 234 / 259 / 226 Clean reads all lobes:105/385 (27.3%)
	Emphysema score (0-600)	ICC: 0.50 (0.42 – 0.57)	≥25 points	18	R: 335 / 372/ 364 L: 339 / 375 / 363 Clean reads all lobes:291/385 (75.6%)
	Emphysematoid destruction score (0-600) †	ICC: 0.27 (0.18 – 0.36)	≥15 points	18	R: 379 / 380 / 378 L: 374 / 384 / 371 Clean reads all lobes: 346/385 (89.9%)
	Cavities score (0-600)	ICC: 0.81 (0.77-0.84)	≥25 points	23	R: 344 / 378 / 370 L: 349 / 380 / 375 Clean reads all lobes: 301/385 (78.2%)
	Normal lung score (0-600)	ICC: 0.80 (0.76 – 0.83)	≥170 points	21	R:183 / 161 / 172 L: 196 / 208 /186 Clean reads all lobes: 73/385(19.0%)
Bronchiectasis	Whole lung bronchiectasis extent score (0-16)	Weighted kappa: 0.72 (0.05)	≥6 points	20	R: 296 / 340/ 324 L: 297 / 337 / 321 Clean reads all lobes: 195/385 (50.7%)
	Whole lung bronchiectasis severity score (0-18)	Weighted kappa: 0.66 (0.05)	≥6 points	25	R: 281 / 315 / 299 L: 266 / 307 / 292 Clean reads all lobes: 133/385 (34.6%)
	Whole lung bronchiectasis pattern score (0-18)*	Weighted kappa: 0.67 (0.05)	≥6 points	20	R: 41/78 (52.6%); 7/15 (46.7%); 16/35 (45.7%) L: 42/80 (52.5%); 29/39 (74.4%); 25/39 (64.1%)
	Whole lung presence / absence of bronchiectasis ‡	N/a	All with discrepancy	79	N/a
	Number of lobes affected (0-6) ‡	N/a	≥3 lobes	30	N/a
Cavities / cystic airspaces	Whole lung cavity /cystic airspace extent score (0-18)	Weighted kappa: 0.65 (0.04)	≥4 points	23	R: 359 / 383 / 372 L: 362 / 380 / 371 Clean reads all lobes: 327/385 (84.9%)
	Whole lung presence / absence of cavities or cystic airspaces ‡	N/a	All with discrepancy	58	N/a
	Whole lung presence / absence of mycetoma	Kappa: 0.49 (0.05)	All with discrepancy	10	R: 98/100 (98.0%); 16/16 (100%); 32/32 (100%) L: 103/105 (98.1%); 25/26 (96.2%); 44/44 (100%)
	Maximum cavity size (size in mm)	N/a	≥22mm	20	N/a
	Parenchymal change allocated to cavities/cystic	N/a	≥10% parenchyma in lobe	7	N/a

	airspaces, but no cavities seen, in at least 1 lobe [§]				
	Cavity seen, but no % parenchyma allocated, in at least 1 lobe [§]	N/a	≥10mm cavity seen in lobe	26	N/a
Nodules	Whole lung nodule extent score (0-18)	Weighted kappa: 0.65 (0.05)	≥5	22	R: 267 / 320 / 304 L: 274 / 315/ 291 Clean reads all lobes: 115/385 (29.9%)
Other airway variables	Whole lung tree in bud severity score (0-18)	Weighted kappa: 0.45 (0.04)	≥9	20	R: 217 / 247 / 226 L: 219 / 248 / 225 Clean reads all lobes: 67/385 (17.4%)
	Whole lung airway plugging severity score (0-18)	Weighted kappa: 0.51 (0.05)	≥5	18	R: 284 / 328 / 302 L: 280 / 313 / 313 Clean reads all lobes: 153/385 (39.7%)
	Whole lung bronchial wall thickening severity score (0-18)	Weighted kappa: 0.42 (0.05)	≥8	22	R: 193 / 248 / 228 L: 198 / 226 / 205 Clean reads all lobes: 73/385 (19.0%)
Whole lung variables	Presence /absence of pleural pathology [‖]	Kappa: 0.60 (0.05)	N/a	0	368/385 (95.6%)
	Presence /absence of lymphadenopathy[‖]	Kappa: 0.17 (0.05)	N/a	0	339/385 (88.1%)
All variables	Total number of CT scans requiring consensus review of ≥1 lobe		239 scans		

[†] Term derived from TB imaging literature, and not Fleischner defined.

*Bronchiectasis pattern is an ordinal variable, but lobar scores treated as nominal and summed / compared to identify scans for consensus review only.

[‡] Derived measures of pathology, for which no measures of inter-reader agreement were calculated.

[§] Discrepancies within scoring tool, with differences in the reporting of the extent of cavities / cystic airspaces between sections.

[‖] No consensus review performed: final scores derived from a single reader only (pleural pathology), or data not used given very low levels of inter-reader agreement (lymphadenopathy).

[††]Clean reads: lobes with either identical scores from original readers, or score determined by consensus review

Final dataset development

Original and consensus reads were combined to form a single 'final' dataset. Where there was agreement between original readers for a given variable in a given lobe, this score was used as the final data point. Where original readers had disagreed and a consensus review had been performed, the consensus score was used as the final data point. Where original readers had disagreed, but no consensus read was available, the approach taken varied: scores from the original readers were averaged for continuous variables (eg. parenchymal scores), pathology was considered present if either or both original readers felt it to be so for binary scores (eg. mycetoma, pleural pathology),

and random selection of original reads was used for nominal variables which could not be combined (eg. bronchiectasis pattern).

Lobar scores were summed to generate whole-lung level scores for data analysis. This pragmatic approach assumes that the impact of pathology in all lobes is equal, and that each lobe contributes the same volume of parenchyma / pathology to the overall lung, regardless of variation in their true size. Several new variables were derived including: lobar presence / absence scores for airway pathologies (E.g. moderate to severe bronchiectasis was considered present in a lobe if the final score was ≥2), a composite variable for 'destroyed lobes' (≥90% of parenchyma was occupied by atelectasis, parenchymal banding or destroyed by cavities/cystic airspaces), and a % score for the total amount of abnormal parenchyma seen across the lung both with and without mosaicism.

The data collection team and participants remained blind to imaging results until after the final study visit, at which point written imaging reports were provided to each participant, and findings explained to each individual by a respiratory physician.

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Appendix 4: Sample size calculation

An *a priori* definition of severe PTLD was established prior to data analysis, based on parameters known to predict adverse patient outcomes in other chronic lung diseases (bronchiectasis, COPD, and ILD) and consensus discussion between a panel of respiratory and TB researchers and clinicians[1](Table 5). The prevalence of severe PTLD was estimated at between 10-50%. A sample size of 400 was sufficient to determine the prevalence of severe PTLD within this range with +/-5% precision and 95% confidence.

Table E5: Composite *a priori* definition of PTLD

Criteria	PTLD present
Abnormal spirometry OR	Airway obstruction with FEV1/FVC ratio<LLN & FEV1<LLN OR Low FVC with FEV1/FVC ratio≥0.7 & FVC<LLN
Abnormal CT Imaging	Moderate-severe bronchiectasis in ≥3 lobes OR Parenchymal abnormality of ≥1/3 of the lung tissue, excluding mosaicism

LLN: Lower limit of normal, as classified using GLI-2012 reference ranges.

The rationale for the parameters and cut-offs included in the *a priori* definition are given below. The studies on which these findings are based include data from non-TB populations in high-resource settings, but was felt plausible that similar outcomes may be seen in in the post-TB population in Malawi also.

Spirometry criteria:

Use of the LLN to define abnormal spirometry is widely accepted practice.(3) Reduced FEV_1 volumes predict mortality both amongst those with COPD, and the general population, with causes including respiratory failure and cardiovascular disease.(8) Recent data suggest that the FVC may be an

[1] JM, SBS, PM, Professor Jane Carter (Respiratory physician and Associate Professor of Medicine at Brown University (USA), past-president of The International Union Against Tuberculosis and Lung Disease), Dr Jeremiah Chakaya (Respiratory physician, lead of Kenyan National TB Control Programme, past-president of The International Union Against Tuberculosis and Lung Disease)

additional, or even more important, driver of mortality even in the absence of persistent symptoms or an underlying diagnosis of lung pathology.(9, 10) Both airway obstruction with reduced FEV_1, and small lungs with reduced FVC were therefore included.

Imaging criteria:

Bronchiectasis and parenchymal damage are common features of PTLD.(5) Bronchiectasis affecting ≥3 lobes on CT imaging has been associated with hospital admissions and all-cause mortality in previous bronchiectasis cohort studies.(11, 12) Studies developing prognostic tools for patients with emphysema and scleroderma related ILD suggest that a cut-off of 20-30% abnormal parenchyma can help to differentiate between those at low and moderate risk of mortality.(13, 14) Because the relative importance of each pattern of parenchymal pathology in PTLD is not known, a cumulative variable including all patterns of parenchymal pathology was used in the definition given here. The extent of mosaicism, which reflects gas trapping rather than parenchymal damage, was not included.

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Appendix 5: Comparison of baseline study spirometry data with community data

Table E6: Comparison of the age-stratified prevalence estimates of moderate-severe airway obstruction and spirometric restriction within this study cohort, with survey weighted prevalence estimates from the 2013-2014 BOLD study in urban Blantyre.(15) All data standardised using NHANES III Caucasian reference ranges.

Age group (n at baseline/ 1-year)	Mod-severe obstruction FEV/FVC<0.7 and FEV1<80% predicted			Low FVC FEV1/FVC>=0.7 and FVC<80% predicted		
	Post-TB cohort TB Rx completion % (SE)	Post-TB cohort 1-year f'up % (SE)	BOLD data set % (SE)	Post-TB cohort TB Rx completion % (SE)	Post-TB cohort 1-year f'up % (SE)	BOLD data set % (SE)
15-19yrs (n=17/13)	11.8% (7.8%)	15.4% (10.0%)	-	82.4% (9.2%)	61.5% (13.5%)	-
20-29yrs (n=83/77)	4.8% (2.4%)	6.5% (2.8%)	2.4% (1.0%)	71.1% (5.0%)	64.9% (5.4%)	32.7% (4.0%)
30-39yrs (n=160/147)	7.5% (2.1%)	8.8% (2.3%)	2.9% (1.5%)	64.4% (3.8%)	55.8% (4.1%)	42.0% (3.8%)
40-49yrs (n=79/75)	11.4% (3.6%)	16.0% (4.2%)	2.3% (0.9%)	62.0% (5.5%)	41.3% (5.7%)	28.3% (4.4%)
50-59yrs (n=17/15)	11.8% (7.8%)	13.3% (8.8%)	9.8% (2.8%)	17.6% (9.2%)	6.7% (6.4%)	39.4% (6.6%)
60+yrs (n=9/9)	11.1% (10.5%)	33.3% (15.7%)	12.0% (4.4%)	33.3% (15.7%)	33.3% (15.7%)	13.8% (6.4%)

Appendix 6: Clinical and respiratory parameters, stratified by HIV-status

Table E7: Clinical and respiratory parameters measured at TB treatment completion, 6-month and 12-month study visits, stratified by HIV-status [§] (n=403)

Parameter	TB treatment completion			6-month visit			12-month visit		
	HIV-negative (n=159)	HIV-positive (n=244)	p-value	HIV-negative (n=143)	HIV-positive (n=231)	p-value	HIV-negative (n=142)	HIV-positive (n=225)	p-value
Symptom prevalence (n, %) [†]									
Breathlessness									
- Never/only with chest infections	83 (52.2%)	143 (58.6%)	0.069	96 (67.1%)	186 (80.5%)	0.014*	101 (71.1%)	181 (80.4%)	0.086
- Few days per month	65 (40.9%)	95 (38.9%)		40 (28.0%)	38 (16.5%)		35 (24.7%)	40 (17.8%)	
- ≥Several days per week	11 (6.9%)	6 (2.5%)		7 (4.9%)	7 (3.0%)		6 (4.2%)	4 (1.8%)	
Cough									
- Never/only with chest infections	86 (54.1%)	172 (70.5%)	0.002*	106 (74.1%)	177 (76.6%)	0.860	113 (79.6%)	194 (86.2%)	0.233
- Few days per month	66 (41.5%)	68 (27.9%)		31 (21.7%)	45 (19.5%)		26 (18.3%)	27 (12.0%)	
- ≥Several days per week	7 (4.4%)	4 (1.6%)		6 (4.2%)	9 (3.9%)		3 (2.1%)	4 (1.8%)	
Sputum production									
- Never/only with chest infections	109 (68.6%)	190 (77.9%)	0.077	113 (79.0%)	186 (80.5%)	0.940	118 (83.1%)	200 (88.9%)	0.240
- Few days per month	45 (28.3%)	51 (20.9%)		28 (19.6%)	42 (18.2%)		23 (16.2%)	23 (10.2%)	
- ≥Several days per week	5 (3.1%)	3 (1.2%)		2 (1.4%)	3 (1.3%)		1 (0.7%)	2 (0.9%)	
Wheeze									0.235
- Never/only with chest infections	147 (92.5%)	223 (91.4%)	0.823	130 (90.9%)	215 (93.1%)	0.188	134 (94.4%)	218 (96.9%)	
- Few days per month	11 (6.9%)	18 (7.4%)		11 (7.8%)	16 (6.9%)		8 (5.6%)	7 (3.1%)	
- ≥Several days per week	1 (0.6%)	3 (1.2%0		2 (1.4%)	0 (0 %)		0 (0%)	0 (0%)	
Any respiratory symptom, ≥monthly	103 (64.8%)	142 (58.2%)	0.186	62 (43.4%)	75 (32.5%)	0.034*	55 (38.7%)	57 (25.3%)	0.007*
Symptom impact (n, %)									
Self-reported impact of chest on activities									
- Does not stop any activities	77 (48.4%)	122 (50.0%)	0.837	108 (75.5%)	181 (78.4%)	0.578	108 (76.1%)	187 (82.1%)	0.241
- Prevents 1-2 activities	67 (42.1%)	97 (39.8%)		27 (28.9%)	41 (17.8%)		28 (19.7%)	28 (12.4%)	
- Prevents most / all activities	15 (9.4%)	25 (0.10%)		8 (5.6%)	9 (3.9%)		6 (4.2%)	10 (4.4%)	
Self-reported impact of chest on work									
- Does not affect work	95 (59.8%)	146 (59.8%)	0.964	115 (80.4%))	192 (83.1%)	0.797	122 (85.9%)	200 (88.9%)	0.022
- Interferes with / made me change work	58 (36.5%)	90 (36.9%)		24 (16.8%)	33 (14.3%0		20 (14.1%)	18 (8.0%)	
- Made me stop work	6 (3.8%)	8 (3.3%)		4 (2.8%)	6 (2.6%)		0 (0%)	7 (3.1%)	
Breathless at rest / during personal care	0 (0%)	2 (0.8%)	0.253	1 (0.7%)	1 (0.4%)	0.731	1 (0.7%)	1 (0.4%)	0.742
Walks slower than peers / stops for rest at own pace	45 (28.5%)	62 (25.5%)	0.512	26 (18.2%)	31 (13.4%)	0.213	28 (19.7%)	35 (15.6%)	0.303
Breathless on hills	79 (50.0%)	96 (39.5%)	0.038*	42 (29.4%)	39 (16.9%)	0.004*	40 (28.2%)	42 (18.9%)	0.033*
Quality of life									
Self-reported general health (n, %)									
- Poor/fair	45 (28.3%)	70 (28.7%)	0.933	23 (16.1%)	30 (13.0%)	0.404	9 (6.3%)	13 (5.8%)	0.826
- Good/excellent	114 (71.7%)	174 (71.3%)		120 (83.9%)	201 (87.0%)		133 (93.7%)	212 (94.2%)	
SGRQ Total score (median, IQR)	10.3 (1.8 – 24.7)	8.2 (0.9 – 22.4)	0.1135	1.1 (0.4 – 16.4)	0.4 (0.0 – 7.3)	0.1043	0.4 (0 – 11.6)	0.4 (0 – 4.6)	0.1300
SGRQ Symptom score (median, IQR)	13.7 (2.7 – 28.8)	10.3 (2.7 – 21.8)	0.0185*	2.7 (0 – 21.9)	2.7 (0 – 10.7)	0.0991	2.7 (0 – 21.4)	2.7 (0 – 10.3)	0.1204

SGRQ Activity score (median, IQR)	12.2 (0 – 41.4)	11.2 (0 – 35.2)	0.1212	0 (0 – 24.1)	0 (0 – 11.2)	0.0279*	0 (0 - 18.2)	0 (0 – 0)	0.0994
SGRQ Impact score (median, IQR)	7.3 (0 – 15.5)	5.5 (0 – 15.0)	0.2777	0 (0 – 7.3)	0 (0 – 5.6)	0.1411	0 (0 – 5.6)	0 (0 – 1.6)	0.0214*
Clinical observations									
BMI (kg/m^2) (median, IQR)	20.3 (18.8 – 21.7)	20.7 (19.0 – 22.6)	0.0471*	20.5 (19.0 – 22.1)	21.2 (19.6 – 23.3)	0.0055*	20.7 (19.2 – 22.5)	21.5 (19.6 – 23.8)	0.0060*
Oxygen saturations (%) (median, IQR)	98 (97 – 99)	98 (98-99)	0.0042*	98 (97-98)	98 (97 – 99)	0.0327*	98 (97-98)	98 (97 – 98)	0.2691
Hypoxaemia (sats <92%) (n, %)	4 (2.5%)	2 (0.8%0	0.169	4 (2.8%)	2 (0.9%)	0.149	3 (2.1%)	1 (0.4%)	0.134
Respiratory rate (breaths/minute) (median, IQR)	19 (17 – 20)	18 (17 – 20)	0.9749	19 (18 – 21)	19 (18 – 21)	0.3201	20 (19 – 22)	20 (19 – 22)	0.8404
Heart rate (beats/minute) (median, IQR)	73 (64 – 86)	82 (72 – 91)	0.0000*	73 (65 – 86)	77 (69 – 86)	0.0117*	73 (6 3- 84)	78 (70 – 87)	0.0004*
Pedal oedema (n, %)	1 (0.6%)	6 (2.5)	0.169	1 (0.7%)	2 (0.9%)	0.861	0 (0%)	3 (1.3%)	0.167
Palatal Kaposi Sarcoma (n=368) (n, %)	2 (1.4%)	6 (2.7%)	0.418	1 (0.7%)	9 (3.9%)	0.063	0 (0.0%)	1 (0.4%)	0.426
Blood tests									
Haemoglobin (g/dL) (median, IQR)	14.6 (13.3 – 15.6)	13.1 (11.7 – 14.5)	0.0000*						
Positive aspergillus IgG ELISA	1 (0.6%)	2 (0.8%)	0.828				0 (0%)	2 (0.8%)	0.252
6-minute walk test (n=395 / 355)									
Distance (m) (mean, sd)	576 (524 – 627)	570 (508 – 617)	0.3360				624 (576 – 663)	606 (564 – 654)	0.1149
Spirometry (n=365 / 341 / 336) ‡									
FEV_1 z-score (mean, sd)	-1.27 (1.33)	-0.94 (1.19)	0.0146*	-1.17 (1.33)	-0.74 (1.17)	0.0019*	-1.15 (1.28)	-0.70 (1.10)	0.0007*
FVC z-score (mean, sd)	-1.08 (1.29)	-0.80 (1.18)	0.0374*	-0.92 (1.29)	-0.50 (1.10)	0.0013*	-0.86 (1.16)	-0.44 (1.02)	0.0006*
FEV_1/FVC ratio z-score (mean, sd)	-0.47 (1.40)	-0.32 (1.15)	0.2492	-0.54 (1.49)	-0.49 (1.14)	0.7310	-0.62 (1.45)	-0.49 (1.19)	0.3728
Pattern of spirometry - Obstruction (FEV1/FVC ratio <LLN) - Low FVC (FEV1/FVCratio≥LLN & FVC<LLN) - Normal (FEV1/FVC ratio ≥LLN & FVC≥LLN)	 27 (19.0%) 36 (25.4%) 79 (55.6%)	 25 (11.3%) 37 (16.7%) 159 (72.0%)	 0.006*	 29 (22.7%) 23 (18.0%) 76 (59.4%)	 31 (14.6%) 22 (10.4%) 159 (75.0%)	 0.010*	 28 (21.9%) 23 (18.0%) 77 (60.2%)	 31 (15.0%) 20 (9.7%) 156 (75.4%)	 0.011*
CXR findings (n=403 / 361)									
% Abnormal parenchyma (median, IQR)	4.6 (0.8 – 13.3)	1.7 (0 – 7.9)	0.0000*				4.0 (0.8 – 10.8)	1.0 (0.0 – 5.0)	0.0000*
Ring and tramline severity score (0-18) (median, IQR)	2.0 (0.0 – 3.5)	0.5 (0.0 – 2.5)	0.0005*				1.5 (0.0 – 3.0)	0.5 (0.0 – 2.0)	0.0065*

*Statistically significant difference between HIV-positive and negative groups, at p<0.05 level.

†Symptom questions derived from SGRQ: Over the past 3-months I have (had shortness of breath / coughed / brought up sputum / had attacks of wheezing): not at all / only with chest infections / a few days a month / several days a week / most days a week; If you have tried to work in the past 3-months: my chest trouble does not affect my work / my chest trouble interferes with my work or made me change my work / my chest trouble made me stop work; Which of these statements best describes how your chest affects you: It does not stop me doing anything I would like to do / It stops me doing 1-2 things I would like to do / it stops me doing most of the things I would like to do / It stops me doing everything I would like to do.

‡ BOLD standard data available for n=365/405 at baseline, n=341/376 at 6-months, and n=336/368 at 12-month study visits. Data age / sex / height standardised using GLI 2012 African American reference ranges to generate z-scores.

§ Data compared between HIV groups using Chi^2 for categorical, and Student's t-test / Wilcoxon rank sum for continuous variables.

Appendix 7: CT imaging data, stratified by HIV-status

Table E8: Final CT imaging data, generated from original and consensus reads, stratified by HIV status (n=383 individuals)

Pathology	All scans (n=385) Median (IQR) [Full range], or N (%)	HIV-negative (n=148) Median (IQR) [Full range] or N (%)	HIV-positive (n=235) Median (IQR) [Full range] or N (%)	p-value
% parenchymal pathology , whole lung level				
Atelectasis and banding	7.5 (2.9 – 14.2) [0.0 – 53.3]	9.2 (5.8 – 17.5) [0.0 – 53.5]	5.8 (2.5 – 11.7) [0.0 – 43.3]	0.0000*
Cavities / cystic air spaces	0.0 (0.0 – 1.7) [0.0 – 46.7]	0.8 (0.0 – 2.7) [0.0 – 46.7]	0.0 (0.0 – 0.8) [0.0 – 27.5]	0.0001*
Mosaicism	5.4 (0.8 – 14.2) [0.0 – 54.2]	6.7 (2.1 – 15.2) [0.0 – 42.1]	4.6 (0.4 –12.5) [0.0 – 54.2]	0.0240*
Emphysema	0.0 (0.0 – 0.8) [0.0 – 71.7]	0.0 (0.0 – 0.4) [0.0 – 64.2]	0.0 (0.0 – 0.8) [0.0 – 71.7]	0.0161*
Ground glass	0.0 (0.0 – 0.8) [0.0 – 45.0]	0.0 (0.0 – 0.8) [0.0 – 27.5]	0.0 (0.0 – 0.8) [0.0 – 45.0]	0.2759
Consolidation	0.8 (0.0 – 2.1) [0.0 – 18.3]	0.8 (0.0 – 2.1) [0.0 – 18.3]	0.8 (0.0 – 2.1) [0.0 – 12.5]	0.1279
Emphysematous destruction	0.0 (0.0 – 0.4) [0.0 – 27.5]	0.0 (0.0 – 0.8) [0.0 – 20.0]	0.0 (0.0 – 0.4) [0.0 – 27.5]	0.1186
Total abnormal parenchyma, any pattern	22.9 (9.2 – 39.2) [0.0 – 100.0]	30.0 (13.5 –41.0) [0.0 – 100.0]	18.3 (6.7– 37.9) [0.0 – 95.8]	0.0003*
Total abnormal parenchyma, excluding mosaicism[†]	12.1 (5.0 – 25.0) [0.0 – 100.0]	15.6 (7.9 – 30.0) [0 – 100.0]	10.0 (3.8 – 21.7) [0 – 90.0]	0.0003*
Number of 'destroyed' lobes [‡] - 0 - 1-2 - 3	 349 (90.7%) 33 (8.6%) 3 (0.8%)	 126 (85.1%) 19 (12.8%) 3 (2.0%)	 222 (94.5%) 13 (5.5%) 0 (0%)	0.009*
Airway scores, whole lung level				
Bronchiectasis extent score (0-16)	2.5 (0.5 – 4.5) [0.0 – 15.5]	3.0 (2.0 – 5.5) [0 – 15.5]	1.5 (0.0 – 4.) [0.0 – 13.5]	0.0000*
Bronchiectasis severity score (0-18)	2.5 (0.5 – 5.0) [0.0 – 15.5]	3.5 (1.5 – 6.0) [0.0 – 15.5]	2.0 (0.0 – 4.0) [0.0 – 14.5]	0.0000*
Bronchial wall thickening severity score (0-18) (n=327) [§]	3.0 (1.5 – 5.5) [0.0 – 14.5]	3.0 (1.5 – 5.5) [0.0 – 13.5]	3.0 (1.0 – 6.0) [0.0 – 14.5]	0.3883
Tree in bud severity score (0-18)	3.5 (1.5 – 6.0) [0.0 – 17.0]	4.5 (2.5 – 6.5) [0.0 – 14.5]	3.0 (1.0 – 6.0) [0.0 – 17.0]	0.0006*
Airway plugging severity score (0-18)	1.0 (0.0 – 2.0) [0.0 – 12.0]	1.0 (0.5 – 2.5) [0.0 – 9.0]	1.0 (0.0 – 2.0) [0.0 – 12.0]	0.0196*
Number of lobes with moderate – severe bronchiectasis ** - 0 - 1-2 - ≥3	 215 (55.8%0 141 (36.6%) 29 (7.5%)	 65 (43.9%) 71 (48.0%) 12 (8.1%)	 149 (63.4%) 69 (29.4%) 17 (7.2%)	0.001*
Any moderate – severe cystic bronchiectasis [††]	49 (12.7%)	28 (18.9%)	20 (8.5%)	0.0030*
Other variables, whole lung level [‡‡]				
Mycetoma present	5 (1.3%) [§§]	4 (2.7%)	1 (0.4%)	0.0560
Nodules present	228 (59.2%)	88 (59.5%)	139 (59.2%)	0.1540
Pleural pathology (effusions or thickening) present	31 (8.1%)	12 (8.1%)	19 (8.1%)	0.9940

*Statistically significant difference between HIV-positive and negative groups, at p<0.05 level.

[†]Mosaicism excluded as represents areas with gas trapping or impaired perfusion rather than primary parenchymal pathology, and can be observed in 'normal' health adults.

[‡] Destroyed lobe: lobe with ≥90% of parenchyma is occupied by banding, atelectasis, or cavities / cystic airspaces.

§ Data missing where extensive parenchymal pathology in ≥1 lobe prevented evaluation of bronchial wall thickness – those with missing data had more abnormal parenchyma (median 46.3% vs. 18.8% in th, p<0.001) and a lower prevalence of HIV-infection (35.9% vs. 54.0%, p=0.004) compared to those with data for this variable.

** Present if average lobar severity score between two readers, or consensus score, was ≥2, so on average bronchial lumen considered to be 2-3 times adjacent vessel diameter in these lobes.

†† Present if moderate to severe bronchiectasis seen in at least 1 lobe, and pattern here deemed to be cystic based on initial agreement between readers or consensus review of scans, or random selection of initial reader reports where disagreement seen and no consensus review available.

‡‡Mycetoma / nodules present if confirmed by both original readers or the consensus scorer. Pleural pathology present if reported by either original reader.

§§ All patients with mycetoma had negative aspergillus IgG at TB treatment completion.

Appendix 8: Relationship between symptoms and spirometry and imaging findings, at TB treatment completion

Table E9: Relationship between spirometry and CT parameters, and symptoms and quality of life at TB treatment completion with p-values for association

Symptom / QoL Parameter	Prevalence (n, %)	Spirometry parameters (n=365)			CT imaging parameters (median, IQR) (n=385)		
		FEV_1 z-score (mean, SD)*	FVC z-score (mean, SD)*	FEV_1/FVC ratio z-score (mean, SD)*	Bronchiectasis severity score (0-18) (median, IQR)†	% abnormal parenchyma (median, IQR) †	Presence of ≥1 destroyed lobe (n, %, 95% CI)‡
Breathlessness							
- Never/only with chest infections	227 (56.0%)	-0.86 (1.18)	-0.72(1.17)	-0.31 (1.09)	2.5 (1.0 – 4.5)	21.9 (9.2 – 35.4)	16 (7.3%) (4.3 -11.6%)
- ≥ Few days per month	178 (44.0%)	-1.32 (1.31)	-1.14 (1.27)	-0.45 (1.44)	2.5 (0.5 – 5.5)	27.1 (9.6 – 42.9)	20 (12.0%) (7.5 -17.9%)
		p<0.001	p=0.001	p=0.287	p=0.440	p=0.070	p=0.051
Cough							
- Never/only with chest infections	259 (64.0%)	-0.94 (1.22)	-0.84 (1.18)	-0.24 (1.23)	2.0 (0.5 – 4.5)	18.8 (7.1 – 35.0)	13 (5.3%) (2.9-8.9%)
- ≥ Few days per month	146 (36.0%)	-1.27 (1.30)	-1.02 (1.31)	-0.61 (0.11)	3.0 (1.0 – 5.5)	31.3 (12.9 – 48.3)	23 (16.4%) (10.7-23.6%)
		p=0.015	p=0.176	p=0.006	p=0.014	P<0.001	p<0.001
Sputum production							
- Never/only with chest infections	300 (74.1%)	-1.01 (1.23)	-0.89 (1.19)	-0.26 (1.26)	2.0 (0.5 – 4.50)	20.8 (8.3 – 38.8)	24 (8.4%) (5.5-12.3%)
- ≥ Few days per month	105 (25.9%)	-1.22 (1.33)	-0.94 (1.34)	-0.68 (0.12)	2.5 (1.0 – 5.25)	28.1 (13.5 – 42.5)	12 (12.0%) (6.4-20.0%)
		p=0.156	p=0.728	p=0.005	p=0.089	p=0.009	p=0.558
Wheeze							
- Never/only with chest infections	372 (91.8%)	-1.05 (1.26)	-0.92 (1.20)	-0.33 (1.22)	2.5 (0.5 – 5.0)	24.2 (9.2 – 39.6)	34 (9.6%) (6.7-13.1%)
- ≥ Few days per month	33 (8.2%)	-1.23 (1.33)	-0.72 (0.30)	-0.88 (0.29)	2.0 (0.5 – 3.0)	20.4 (9.6 – 38.8)	2 (6.7%) (0.8-22.1%)
		p=0.451	p=0.4071	p=0.0260	p=0.220	p=0.850	p=0.599
Any respiratory symptom							
- Never/only with chest infections	159 (39.3%)	-0.79 (1.19)	-0.68 (1.17)	-0.25 (1.12)	2.0 (0.5 – 4.0)	18.3 (7.1 – 34.6)	7 (4.6%) (1.9-9.3%)
- ≥ Few days per month	246 (60.7%)	-1.23 (1.28)	-1.05 (1.25)	-0.45 (1.34)	2.5 (0.5 – 5.0)	27.3 (10.0-42.9)	29 (12.4%) (8.5-17.3%)
		p=0.001	p=0.013	p=0.130	p=0.349	p=0.002	p=0.011

*Student's t-test; †Wilcoxen rank sum test; ‡Chi-square test

Appendix 9: Multi-level linear regression models for change in spirometry over time

Table E10: Multi-level linear regression, to investigate parameters predicting spirometry values in the first year after TB treatment completion[†] (n=347).[‡]

Variable measured at TB treatment completion	Univariate (ml, 95% CI)	Multivariate, partial model (ml, 95% CI)	Multivariate, full model (ml, 95% CI)
Absolute FEV_1 (ml) over follow-up period			
Time from TB treatment end [§]			
6-months	66.70 (47.39 – 86.01)*	62.17 (41.78 – 82.56)*	65.30 (45.00 – 85.61)*
12-months	72.73 (48.26 – 97.19)*	65.57 (39.47 – 91.68)*	70.56 (44.58 – 96.54)*
HIV positive status	197.57 (83.03 – 312.11)*	193.75 (79.43 – 308.08)*	98.61 (-2.01 – 199.22)
Microbiologically proven TB	-61.81 (-194.79 – 71.17)	-9.12 (-140.23 – 121.99)	30.82 (-84.35 – 145.98)
BMI (kg/m2)	18.32 (9.26 – 27.38)*	7.39 (-1.96 – 16.74)	2.20 (-7.01 – 11.40)
Pack-year smoking history	-7.90 (-20.00 – 4.20)	-4.90 (-16.79 – 7.00)	-0.75 (-11.15 – 9.65)
Maximum education ≤ 1ry school	-108.59 (-225.94 – 8.76)	-108.26 (-224.69 – 8.18)	-37.49 (-139.97 – 64.99)
Respiratory symptoms ≥monthly	-198.98 (-310.07 - -87.90)*		-111.26 (-208.10 - -14.43)*
Bronchiectasis severity score (0-18) – 3-point increments [‖]	-221.04 (-270.18 - -171.91)		-95.56 (-155.64 - -35.47)*
Abnormal parenchyma (%) – 10% increments **	-152.87 (-180.38 - -125.36)		-106.40 (-141.38 - -71.4)*
Variance components (% of model variance): change over time		*1.85%*	*2.53%*
Variance components (% of model variance): baseline FEV1		*94.22%*	*92.05%*
Absolute FVC (ml) over follow-up period			
Time from TB treatment end §			
- 6-months	124.49 (100.70 – 148.30)*	111.77 (87.04 – 136.50)*	115.38 (90.72 – 140.05)*
- 12-months	145.63 (117.66 – 173.59)*	125.21 (95.26 – 155.16)*	131.28 (101.41 – 161.15)*
HIV positive status	197.30 (75.42 – 319.18)*	184.22 (64.02 – 304.43)*	92.94 (-18.17 – 204.04)
Microbiologically proven TB	-18.24 (-159.57 – 123.09)	30.45 (-107.28 – 168.17)	65.99 (-61.11 – 193.09)
BMI (kg/m2)	40.58 (29.97 – 51.19)*	21.34 (10.73 – 31.94)*	15.35 (4.75 – 25.95)*
Pack-year smoking history	-6.04 (-18.88 – 6.81)	-4.38 (-16.86 – 8.10)	-1.87 (-13.34 – 9.59)
Maximum education ≤ 1ry school	-1.34 (-126.72 – 124.04)	-2.97 (-125.46 – 199.51)	63.45 (-49.78 – 176.68)
Respiratory symptoms ≥monthly	-200.30 (-318.52 - -82.08)*		-123.61 (-230.53 - -16.69)*
Bronchiectasis severity score (0-18) – 3-point increments [‖]	-217.87 (-271.12 - -164.62)*		-133.62 (-200.01 - -67.23)*
Abnormal parenchyma (%) – 10% increments **	-131.74 (-162.76 - -100.73)*		-67.03 (-105.67 - -28.39)*
Variance components (% of model variance): change over time		*1.60%*	*2.01%*
Variance components (% of model variance): baseline FVC		*93.18%*	*91.26%*

* OR statistically significant at p<0.05 level.

[†] Model construction based on apriori selection of risk-factors / confounders, and elimination of co-linear variables. Interactions with time evaluated. All univariate & multivariate models coefficients represent the average change in FEV1 or FVC (ml) expected for a 1-unit change in the predictor, holding all other parameters still, and include adjustment for participant age (years), sex, and height (cm).

‡ Participants excluded if absent HIV status at TB treatment completion (n=2), no valid baseline spirometry (n=36), no baseline HRCT imaging (n=20). Includes participants contributing either 6-month (n=13) or 12-month (n=322) follow-up.

§ Negative correlation identified between FEV1 and time (partial model: -0.46 (-0.58 - -0.31) / full model: -0.37 (-0.51 - -0.21)) and FVC and time (partial model: -0.56 (-0.68 - -0.40)/ full model: -0.44 (-0.59 - -0.26)) in all models.

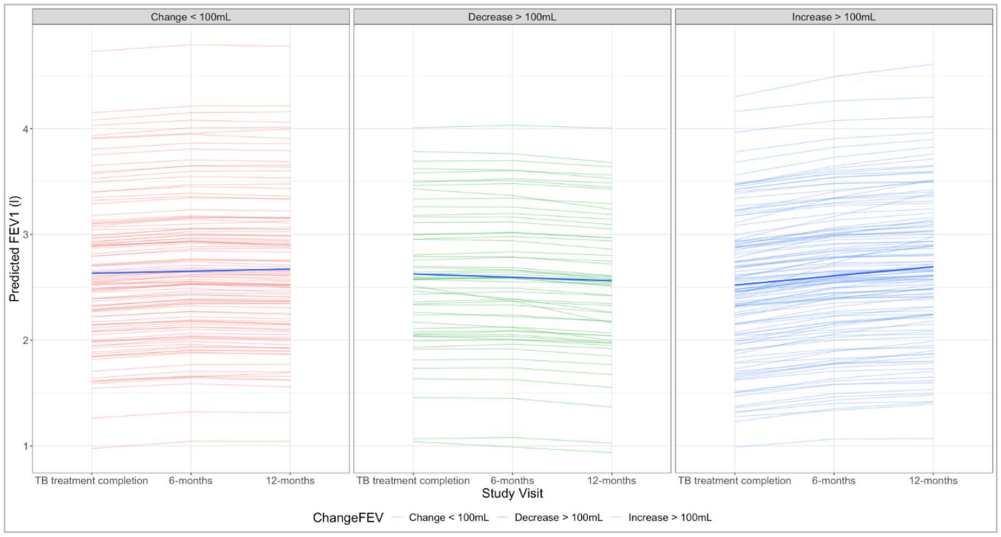
‖ Bronchiectasis severity score (0-18): unweighted sum of 6x lobar bronchiectasis scores ranging from 0 (no bronchiectasis) to 3 (severe dilatation >3 times diameter of adjacent vessel), such that increment of 3 points represents one additional lobe with severe airway dilatation, or combination of 1-3 lobes with less severe disease.

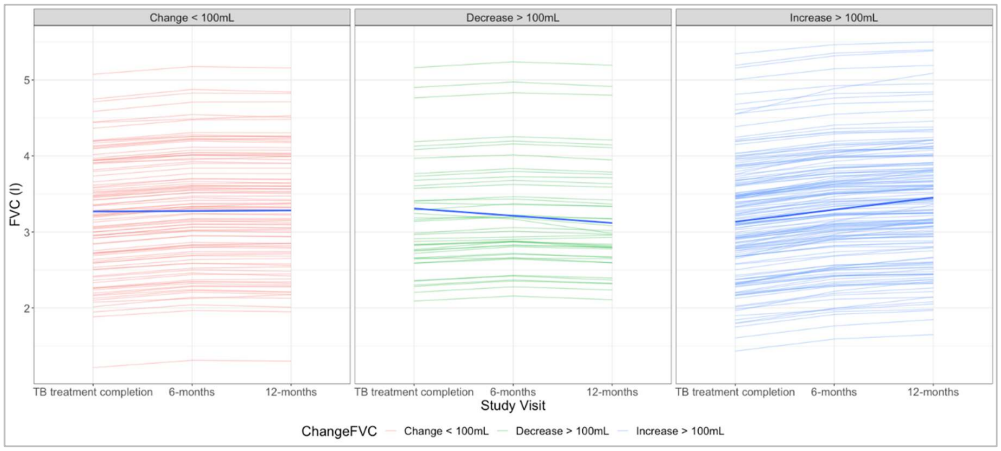
** Total % of parenchymal abnormalities across lung, including: parenchymal banding, atelectasis, consolidation, ground glass change, emphysema, emphysematoid destruction, cavities / cystic airspaces. Excluding mosaicism which represents airway/vascular rather than lung tissue abnormality.

Appendix 10: Predicted change in Spirometry over time

Figure E3: Predicted FEV_1 and FVC volumes at TB treatment completion, and trajectories of change over 1-year, derived from multi-level linear regression models and controlling for patient characteristics, baseline symptoms, and baseline structural lung pathology.

Stratification according to observed change relative to the minimally important clinical difference (MCID) of 100ml.





Appendix 11: Factors predicting chronic respiratory symptoms at 1-year, including sensitivity analyses

Table E11: Logistic regression models of baseline parameters associated with the presence of chronic respiratory symptoms[†] at 1-year (n=325)[‡].

Variables measured at TB treatment end	Univariate, OR (95% CI)	Multivariate, controlling for baseline FEV_1[§] OR (95% CI)	Multivariate, controlling for baseline FVC [§] OR (95% CI)
Age (yrs)	0.99 (0.97 – 1.02)	0.98 (0.95 – 1.01)	0.99 (0.96 – 1.01)
Female sex	1.64 (1.00 – 2.70)*	0.63 (0.27 – 1.46)	0.73 (0.31 – 1.71)
Height (cm)	0.96 (0.93 – 0.99)*	0.98 (0.94 – 1.03)	0.97 (0.93 – 1.02)
HIV status - Negative - Positive, CD4≥200 - Positive, CD4<200	 1.0 0.46 (0.26 – 0.79)* 0.53 (0.29 – 0.98)*	 1.0 0.33 (0.18 – 0.63)* 0.40 (0.19 – 0.84)*	 1.0 0.33 (0.18 – 0.62)* 0.38 (0.18 – 0.80)*
Microbiologically proven TB	0.80 (0.46 – 1.40)	0.74 (0.40 – 1.39)	0.74 (0.40 – 1.38)
BMI (kg/m2)	1.01 (0.93 – 1.10)	1.08 (0.98 – 1.19)	1.08 (0.98 – 1.19)
Hb (g/dL)	0.88 (0.78 – 0.995)*	0.82 (0.70 – 0.98)*	0.82 (0.70 – 0.98)*
Pack-year smoking history	0.98 (0.93 – 1.04)	0.98 (0.93 – 1.04)	0.98 (0.93 – 1.04)
Maximum education ≤ 1ry school	1.28 (0.79 – 2.06)	1.18 (0.67 – 2.08)	1.24 (0.71 – 2.17)
Respiratory symptoms ≥monthly	2.74 (1.62 – 4.64)*	2.42 (1.37 – 4.27)*	2.45 (1.39 – 4.32)*
Absolute FEV1 (100 ml increments)	0.93 (0.89 – 0.96)*	0.95 (0.89 – 1.00)	
Absolute FVC (100 ml increments)	0.95 (0.92 – 0.98)*		0.98 (0.93 – 1.03)
Bronchiectasis severity score (3-point increments, 0-6) [‖]	1.08 (0.86 – 1.36)	0.88 (0.63– 1.22)	0.89 (0.64 – 1.25)
Abnormal parenchyma (10% increments) [††]	1.14 (1.01 – 1.31)*	1.11 (0.91 – 1.35)	1.16 (0.96 – 1.40)

*OR statistically significant at p<0.05 level.

[†]Cough, breathlessness, sputum production, or wheeze with frequency ≥few days/month.

[‡]Participants excluded if absent HIV status at TB treatment completion (n=2), no valid baseline spirometry (n=36), no baseline HRCT imaging (n=20), or no symptom data available at 12-month study visit (n=22).

[§]Co-linearity of FEV_1 and FVC precludes inclusion of both in a single model – separate models constructed to control for baseline level of each.

[‖]Bronchiectasis severity score (0-18): unweighted sum of 6x lobar bronchiectasis scores ranging from 0 (no bronchiectasis) to 3 (severe dilatation >3 times diameter of adjacent vessel), such that increment of 3 points represents one additional lobe with severe airway dilatation, or combination of 1-3 lobes with less severe disease.

[††]Total % of parenchymal abnormalities across lung, including: parenchymal banding, atelectasis, consolidation, ground glass change, emphysema, emphysematoid destruction, cavities / cystic airspaces. Excluding mosaicism which represents airway/vascular rather than lung tissue abnormality.

Table E12: Sensitivity analyses of logistic regression models of baseline parameters associated with the presence of chronic respiratory symptoms † at 1-year (n=347) ‡, with outcomes for those lost to follow-up allocated as positive or negative.

'All symptomatic' models: All participants with missing 1-year symptom data assumed to have ongoing respiratory symptoms (n=22)

'None symptomatic' models: All participants with missing 1-year data assumed to have no ongoing respiratory symptoms (n=22)

Variables measured at TB treatment end	Multivariate model, with FEV_1		Multivariate model, with FVC	
	All symptomatic	None symptomatic	All symptomatic	None symptomatic
Age (yrs)	0.98 (0.95 – 1.01)	0.99 (0.96 – 1.02)	0.98 (0.96 – 1.01)	0.99 (0.97 – 1.02)
Female sex	0.75 (0.34 – 1.65)	0.69 (0.30 – 1.56)	0.87 (0.39 – 1.94)	0.77 (0.34 – 1.76)
Height (cm)	1.00 (0.96 – 1.04)	0.98 (0.93 – 1.02)	0.99 (0.95 – 1.03)	0.97 (0.93 – 1.01)
HIV status - Negative - Positive, CD4≥200 - Positive, CD4<200	 1.0 0.32 (0.18 – 0.59)* 0.50 (0.25 – 1.00)	 1.0 0.39 (0.21 – 0.72)* 0.41 (0.20 – 0.84)*	 1.0 0.32 (0.17 – 0.58)* 0.48 (0.24 – 0.96)*	 1.0 0.38 (0.21 – 0.71)* 0.39 (0.19 – 0.80)*
Microbiologically proven TB	0.79 (0.44 – 1.43)	0.75 (0.41 – 1.39)	0.79 (0.44 – 1.42)	0.75 (0.41 – 1.38)
BMI (kg/m2)	1.07 (0.98 – 1.17)	1.08 (0.98 – 1.18)	1.06 (0.97 – 1.17)	1.07 (0.97 – 1.18)
Hb (g/dL)	0.82 (0.70 – 0.96)*	0.88 (0.75 – 1.03)	0.81 (0.70 – 0.95)*	0.88 (0.75 – 1.03)
Pack-year smoking history	0.97 (0.92 – 1.03)	0.99 (0.93 – 1.04)	0.97 (0.92 – 1.03)	0.99 (0.93 – 1.04)
Maximum education ≤ 1ry school	1.07 (0.63 – 1.81)	1.16 (0.67 – 2.00)	1.11 (0.66 – 1.87)	1.21 (0.70 – 2.07)
Respiratory symptoms ≥monthly	2.49 (1.46 – 4.23)*	2.15 (1.23 – 3.75)*	2.54 (1.50 – 4.31)*	2.19 (1.25 – 3.81)*
Absolute FEV1 (100 ml increments)	0.95 (0.90 – 1.00)*	0.96 (0.90 – 1.01)		
Absolute FVC (100 ml increments)			0.99 (0.94 – 1.04)	0.98 (0.94 – 1.03)
Bronchiectasis severity score (3 point increments, 0-6) §	0.84 (0.61 – 1.15)	0.92 (0.66 – 1.27)	0.86 (0.62 – 1.18)	0.93 (0.67 – 1.29)
Abnormal parenchyma (10% increments) ‖	1.10 (0.91 – 1.33)	1.11 (0.92 – 1.34)	1.15 (0.96 – 1.39)	1.15 (0.96 – 1.39)

*OR statistically significant at p<0.05 level.

† Cough, breathlessness, sputum production, or wheeze with frequency ≥few days/month.

‡ Participants excluded if absent HIV status at TB treatment completion (n=2), no valid baseline spirometry (n=36), no baseline CT imaging (n=20).

§ Bronchiectasis severity score (0-18): unweighted sum of 6x lobar bronchiectasis scores ranging from 0 (no bronchiectasis) to 3 (severe dilatation >3 times diameter of adjacent vessel), such that increment of 3 points represents one additional lobe with severe airway dilatation, or combination of 1-3 lobes with less severe disease.

‖Total % of parenchymal abnormalities across lung, including: parenchymal banding, atelectasis, consolidation, ground glass change, emphysema, emphysematoid destruction, cavities / cystic airspaces. Excluding mosaicism which represents airway/vascular rather than lung tissue abnormality.

Appendix 12: Factors predicting acute respiratory events over 1-year, including sensitivity analyses

Table E13: Logistic regression models of baseline parameters associated with the presence of any acute respiratory events[†] over 1-year follow up (n=335)[‡].

Variables measured at TB treatment end	Univariate OR (95% CI)	Multivariate, controlling for baseline FEV_1 [§] OR (95% CI)	Multivariate, controlling for baseline FVC [§] OR (95% CI)
Age	1.01 (0.99 – 1.04)	1.01 (0.98 – 1.04)	1.02 (0.98 -1.05)
Female sex	1.29 (0.71 – 2.36)	0.43 (0.16 – 1.18)	0.43 (0.15 – 1.19)
Height	0.96 (0.92 – 0.99)*	0.96 (0.91 – 1.01)	0.96 (0.91 – 1.02)
HIV status - Negative - Positive, CD4≥200 - Positive, CD4<200	 1.0 0.51 (0.26 – 0.996)* 0.50 (0.23 – 1.06)	 1.0 0.43 (0.20 – 0.90)* 0.34 (0.14 – 0.85)*	 1.0 0.42 (0.20 – 0.89)* 0.33 (0.13 – 0.82)*
Microbiologically proven TB	1.05 (0.52 – 2.11)	1.21 (0.56 – 2.63)	1.23 (0.56 – 2.68)
BMI (kg/m2)	0.98 (0.89 – 1.09)	1.03 (0.91 – 1.15)	1.03 (0.92 – 1.15)
Hb (g/dL)	0.90 (0.78 – 1.04)	0.86 (0.71 – 1.04)	0.86 (0.71 – 1.04)
Pack-year smoking history	0.98 (0.91 – 1.05)	0.98 (0.91 – 1.05)	0.97 (0.91 – 1.05)
Maximum education ≤ 1ry school	1.02 (0.57 – 1.84)	0.81 (0.41 – 1.61)	0.87 (0.44 – 1.70)
Respiratory symptoms ≥monthly	3.00 (1.49 – 6.04)*	2.60 (1.25 – 5.42)*	2.60 (1.25 – 5.42)*
Absolute FEV1 (100 ml increments)	0.94 (0.89 – 0.98)*	0.94 (0.88 – 1.01)	
Absolute FVC (100 ml increments)	0.95 (0.91 – 0.99)*		0.95 (0.89 – 1.02)
Bronchiectasis severity score (3-point increments, 0-6)[‖]	0.94 (0.70 – 1.27)	0.81 (0.54 – 1.22)	0.80 (0.52 – 1.21)
Abnormal parenchyma (10% increments) [††]	1.05 (0.90 – 1.23)	0.99 (0.79 – 1.25)	1.01 (0.80 – 1.27)

*OR statistically significant at p<0.05 level.

[†]Present if ≥1 acute respiratory event (an unscheduled visit to health care provider (outpatient or inpatient) due to a respiratory complaint (cough, breathlessness, sputum, wheeze, chest pain)) during 6- or 12-month study follow-up.

[‡]Participants excluded if absent HIV status at TB treatment completion (n=2), no valid baseline spirometry (n=36), no baseline HRCT imaging (n=20), or no outcome data obtained over follow-up period (n=12). Includes participants contributing either 6-month (n=13) and 12-month (n=322) follow-up.

[§]Co-linearity of FEV_1 and FVC precludes inclusion of both in a single model – separate models constructed to control for baseline level of each.

[‖]Bronchiectasis severity score (0-18): unweighted sum of 6x lobar bronchiectasis scores ranging from 0 (no bronchiectasis) to 3 (severe dilatation >3 times diameter of adjacent vessel), such that increment of 3 points represents one additional lobe with severe airway dilatation, or combination of 1-3 lobes with less severe disease.

[††]Total % of parenchymal abnormalities across lung, including: parenchymal banding, atelectasis, consolidation, ground glass change, emphysema, emphysematoid destruction, cavities / cystic airspaces. Excluding mosaicism which represents airway/vascular rather than lung tissue abnormality.

Table E14: Sensitivity analyses of logistic regression models of baseline parameters associated with the presence of any acute respiratory events† over 1-year follow up‡, with outcomes for those lost to follow-up allocated as positive or negative.

Analysis 1: Participants with 6-months follow-up only, who were not known to have already had a respiratory event, assumed to have had a respiratory event after LTFU (n=335).

Analysis 2: Participants with 6-months follow-up only who were not known to have already had a respiratory event assumed to have had a respiratory event after LTFU, AND those with no follow-up assumed to have had a respiratory event (n=347).

Analysis 3: Participants with no-follow up assumed to have had a respiratory event (n=347).

Variables measured at TB treatment end	Multivariate model, with FEV_1			Multivariate model, with FVC		
	Analyses 1	Analysis 2	Analysis 3	Analyses 1	Analysis 2	Analysis 3
Age	1.00 (0.97 – 1.04)	1.00 (0.97 – 1.03)	1.01 (0.98 – 1.05)	1.01 (0.98 – 1.04)	1.01 (0.98 – 1.04)	1.02 (0.99 – 1.05)
Female sex	0.42 (0.16 – 1.09)	0.60 (0.25 – 1.46)	0.42 (0.16 – 1.15)	0.46 (0.17 – 1.19)	0.65 (0.27 – 1.59)	0.41 (0.15 – 1.15)
Height	0.96 (0.91 – 1.01)	0.99 (0.95 – 1.04)	0.95 (0.90 -1.01)	0.96 (0.91 – 1.01)	0.99 (0.94 – 1.03)	0.96 (0.90 – 1.01)
HIV status - Negative - Positive, CD4≥200 - Positive, CD4<200	1.0 0.39 (0.19 – 0.80)* 0.40 (0.17 – 0.92)*	1.0 0.36 (0.18 – 0.72)* 0.50 (0.24 – 1.07)	1.0 0.44 (0.21 – 0.93)* 0.34 (0.14 – 0.84)*	1.0 0.39 (0.19 – 0.79)* 0.38 (0.17 – 0.88)*	1.0 0.36 (0.18 – 0.71)* 0.49 (0.23 – 1.03)*	1.0 0.44 (0.21 – 0.92)* 0.33 (0.13 – 0.81)*
Microbiologically proven TB	1.44 (0.68 – 3.02)	1.47 (0.73 – 2.94)	1.21 (0.56 – 2.62)	1.43 (0.68 – 3.01)	1.46 (0.73 – 2.93)	1.21 (0.56 – 2.64)
BMI (kg/m2)	1.06 (0.95 – 1.17)	1.03 (0.94 – 1.15)	1.03 (0.91 – 1.15)	1.05 (0.95 – 1.17)	1.04 (0.94 – 1.15)	1.03 (0.92 – 1.15)
Hb (g/dL)	0.84 (0.70 – 1.00)*	0.84 (0.71 – 1.00)*	0.87 (0.72 – 1.05)	0.84 (0.70 – 1.00)	0.84 (0.71 – 1.00)*	0.87 (0.72 – 1.05)
Pack-year smoking history	0.96 (0.89 – 1.04)*	0.95 (0.88 – 1.03)	0.98 (0.91 – 1.05)	0.96 (0.89 – 1.04)	0.95 (0.88 – 1.03)	0.98 (0.91 – 1.05)
Maximum education ≤ 1ry school	0.83 (0.44 – 1.58)	0.78 (0.43 – 1.42)	0.82 (0.41 – 1.61)	0.87 (0.46 – 1.63)	0.81 (0.45 – 1.47)	0.87 (0.44 – 1.69)
Respiratory symptoms ≥monthly	2.33 (1.21– 4.52)*	2.49 (1.34 – 4.63)*	2.45 (1.18 – 5.10)*	2.36 (1.22 – 4.56)*	2.52 (1.35 – 4.68)*	2.46 (1.18 – 5.12)*
Absolute FEV1 (100 ml increments)	0.96 (0.90 – 1.03)	0.96 (0.91 – 1.02)	0.95 (0.89 – 1.02)			
Absolute FVC (100 ml increments)				0.98 (0.93 – 1.04)	0.98 (0.93 – 1.04)	0.96 (0.90 – 1.02)
Bronchiectasis severity score (3 point increments, 0-6) §	0.75 (0.50 – 1.12)	0.77 (0.53 – 1.11)	0.82 (0.54 – 1.23)	0.75 (0.50 – 1.13)	0.77 (0.53 – 1.12)	0.80 (0.52 – 1.22)
Abnormal parenchyma (10% increments) ‖	1.00 (0.80 – 1.25)	1.01 (0.82 – 1.25)	0.99 (0.79 – 1.25)	1.03 (0.83 - 1.28)	1.04 (0.85 – 1.28)	1.01 (0.80 – 1.27)

*OR statistically significant at p<0.05 level.

†Present if ≥1 acute respiratory event (an unscheduled visit to health care provider (outpatient or inpatient) due to a respiratory complaint (cough, breathlessness, sputum, wheeze, chest pain)) documented in health passport +/- self reported during 6- or 12-month study follow-up.

‡Participants excluded if absent HIV status at TB treatment completion (n=2), no valid baseline spirometry (n=36), no baseline CT imaging (n=20), or no outcome data obtained over follow-up period (n=12). Includes participants contributing either 6-month (n=13) and 12-month (n=322) follow-up.

[§] Bronchiectasis severity score (0-18): unweighted sum of 6x lobar bronchiectasis scores ranging from 0 (no bronchiectasis) to 3 (severe dilatation >3 times diameter of adjacent vessel), such that increment of 3 points represents one additional lobe with severe airway dilatation, or combination of 1-3 lobes with less severe disease.
[‖] Total % of parenchymal abnormalities across lung, including: parenchymal banding, atelectasis, consolidation, ground glass change, emphysema, emphysematoid destruction, cavities / cystic airspaces. Excluding mosaicism which represents airway/vascular rather than lung tissue abnormality.

Appendix 13: Factors predicting spirometry at 1-year

Table E15: Linear regression model, to determine the effect of any respiratory events in the 1-year follow up period, on spirometry parameters 1-year following TB treatment completion (n=296)[†].
All univariate & multivariate models coefficients include adjustment for participant age (yrs), sex, and height (cm).

Variables	Univariate (ml, 95% CI)	Multivariate, partial model (ml, 95% CI)	Multivariate, full model (ml, 95% CI)
Absolute FEV_1 (ml) at 1-year			
HIV positive status	192.30 (69.39 – 315.21)*	173.89 (52.57 – 295.20)*	85.04 (35.68 – 134.40)
Microbiologically proven TB	-81.57 (-222.21 – 59.07)	-32.16 (-168.75 – 104.44)	-33.36 (-88.38 – 21.65)
BMI (kg/m2)	41.10 (19.72 – 62.48)*	37.83 (16.79 – 58.88)*	0.93 (-7.95 – 9.81)
Pack-year smoking history	-11.74 (-24.12 – 0.63)	-8.27 (-20.35 – 3.80)	-2.82 (-7.65 – 2.02)
Maximum education ≤ 1ry school	-138.51 (-265.89 - -11.14)*	-128.39 (-253.25 - -3.52)*	-8.25 (-58.89 – 42.38)
Respiratory symptoms ≥monthly	-181.70 (-300.56 - -62.84)*		-9.42 (-57.04 – 38.20)
Absolute FEV1 at baseline (100 ml increments)	87.80 (83.47 – 92.13)*		86.74 (81.62 – 91.86)*
Bronchiectasis severity score (3-point increments, 0-6)	-194.40 (-248.03 - -140.77)*		-5.32 (-35.04 – 24.40)
Abnormal parenchyma (10% increments)	-151.35 (-181.37 - -121.34)*		6.45 (-12.62 – 25.52)
≥1 acute respiratory event during follow-up	-202.91 (-366.66 - -39.17)*		-81.97 (-146.95 - -17.00)*
Absolute FVC (ml) at 1-year			
HIV positive status	181.00 (53.19 – 308.81)*	165.79 (38.00 – 293.58)*	108.55 (55.12 – 161.99)*
Microbiologically proven TB	-1.24 (-147.40 – 144.92)	37.50 (-106.38 – 181.38)	5.49 (-54.15 – 65.13)
BMI (kg/m2)	39.17 (16.92 – 61.42)	36.91 (14.75 – 59.08)*	-4.06 (-13.71 – 5.59)
Pack-year smoking history	-9.43 (-22.29 – 3.43)	-7.72 (-20.44 – 5.00)	-1.35 (-6.59 – 3.89)
Maximum education ≤ 1ry school	-24.09 (-157.17 – 109.00)	-19.29 (-150.82 – 112.24)	22.37 (-32.24 – 76.98)
Respiratory symptoms ≥monthly	-185.13 (-308.45 - -61.82)*		-7.55 (-59.16 – 44.05)
Absolute FVC at baseline (100 ml increments)	84.50 (80.01 – 88.99)*		85.73 (80.71 – 90.74)*
Bronchiectasis severity score (3-point increments, 0-6)	-178.93 (-235.56 - -122.31)*		-14.22 (-46.52 – 18.08)
Abnormal parenchyma (10% increments)	-127.27 (-160.15 - -94.39)*		20.95 (0.94 – 40.97)*
≥1 acute respiratory event during follow-up	-256.72 (-425.66 - -87.77)*		-121.78 (-192.19 - -51.37)*

*Co-efficients statistically significant at p<0.05 level.

[†]Participants excluded if absent HIV status at TB treatment completion (n=2), no valid baseline spirometry (n=36), no baseline HRCT imaging (n=20), no valid 12-month spirometry (n=48), or no data on events obtained over follow-up period (n=12).

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Supplementary Materials

Manuscript title:

Patient outcomes associated with post-tuberculosis lung damage in Malawi: a prospective cohort study

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Meghji J, *et al. Thorax* 2020;0:1–10. doi: 10.1136/thoraxjnl-2019-213808

Appendix 1: CT scanning protocol

All participants were offered low-dose HRCT imaging at pTB treatment completion, except for those with contraindications: absence of informed consent, positive pregnancy test / self-reported current pregnancy, inability to travel to the imaging centre. Those with positive TB symptom screens (cough, weight loss, fever, night sweats, haemoptysis) at pTB-treatment completion were asked to submit sputum, and only booked for imaging if smear negative.

For logistical reasons, 2 imaging centres were used: Blantyre Adventist Hospital (BAH), Blantyre (Feb – Aug 2016) and Kamuzu Central Hospital (KCH), Lilongwe (Nov 2016 – May 2017). The same unenhanced low dose imaging protocol was used at both sites (Table E1). Imaging was performed supine in full inspiration, with coverage from apices to bases. Scans were reconstructed using a lung algorithm only, accepting that this would give limited diagnostic quality for soft tissue. Images were stored in DICOM format electronic files.

Table E1: Non contrast high resolution CT scanning protocol

Topogram

mA	kV	Scan time	Slice	Topogram length	Tube position	Direction	API	Kernel	Window	Tilt
50	120	5.3 sec	1.0 mm	512 mm	Top	Cranio-caudal (Supine)	Inspiration	T20s Standard	Topogram body	0.0°

Scan

Effective mAs	kV	Scan time	Delay	Slice	CTDL Vol	Pitch	Acquisition	Care dose
50 depending on patient size	120 depending on patient size	12.05	5 sec	Volume HRCT 1mm at 1mm intervals	3.90 mGy	1.15	Spiral scan	Care Dose 4D

Processing

Reconstuction	Image order	Reconstruction increment	Kernel	Window	Field of view	Centre X	Centre Y	3D
Axial	Cranial-caudal	1.0mm	B60f	Lung window	380	0 mm	0 mm	VRT & MIP as needed

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Appendix 2: Spirometry quality control procedures

Spirometry measurement

Pre- and post-bronchodilator spirometry were performed at each study visit – each participant performed up to eight attempts for each, until three high quality curves were obtained. Where consistently poor technique / difficulty performing the test was observed, participants were asked to return on another occasion for repeat testing. Salbutamol was administered via a spacer after the pre-bronchodilator tests, using two 100mcg doses from an MDI device. A minimum of 15 minutes was allowed between administration of salbutamol and repeat spirometry. Nose clips were found to function poorly in the study population, so participants were asked to pinch their noses during testing. Disposable spirettes were used and changed for each patient. Testing was performed in the seated position during baseline and 12-month visits, and at the 6-month visit if suitable seating was available. Participant age (years), standing height (mm), and weight (kg) were recorded contemporaneously for standardization of results. Spirometry data were stored electronically using EasyWare software.

Spirometry quality control

All pre- and post- spirometry attempts were reviewed by two readers (JM & LZ) independently, and graded for errors according to the CDC National Institute for Occupational Safety & Health (NIOSH) guidelines, and the BOLD study quality control procedures (Table 2).(1, 2) Tests were reviewed in chronological order in batches of 100, and grading was resolved by consensus discussion in the event of discrepancy. The 5% of usable spirometry readings with the longest Forced Expiratory Times (FET) values, and readings with the 1% highest and lowest FEV_1 and FVC values were manually reviewed, and patient results compared across study visits to ensure consistency and accuracy. Curves which

were clearly inconsistent with other data for a given patient, where a zero-flow error was suspected, or where there was suspicion of an error in study ID or test performance, were classified as invalid.

Table E2: Grading criteria for individual spirometry trials, with source of guidelines listed

Reason for rejection of spirometry curve	Abbreviation for error	Definition of error	Reference/ source
High PEFT	p (PEFT)	PEFT ≥150msecs	BOLD QC requirements, which relaxed the ndd cut off of 120ms
High BEV	b (BEV)	BEV ≥150ml AND BEV ≥5% of FVC	ATS criteria, NIOSH, BOLD QC requirements state that for a curve to be included BEV must be <5% or <150ml, whichever is greater.
Non-maximal effort	e (effort)	Marked lack of peak, indicating weak blast OR Markedly reduced peak compared to other curves, indicating poor filling of lungs at start of test	BOLD QC requirements ATS criteria NIOSH guidelines
Early termination of expiration	t (termination)	Insufficient expiratory phase on volume-time curve – duration of expiration for < 6 secs OR failure to reach plateau of ≥1 sec OR Sharp early drop to 0 on flow-volume curve	BOLD QC requirements ATS criteria NIOSH guidelines
Extra breath	x (extra)	Visible extra breath on flow-volume and or the volume-time curves	BOLD QC requirements NIOSH guidelines
Glottis closure that influences measurement	g (glottis)	Abrupt flat line on volume-time curve, with sharp drop to 0 on flow-volume curve	BOLD QC requirements ATS criteria NIOSH guidelines
Leak	l (leak)	Descent of volume-time curve, after peak is reached, with 'back-track' of flow-volume curve at the end of expiration	BOLD QC requirements ATS criteria NIOSH guidelines
Obstructed mouthpiece	o (obstruction)	Artefact in the flow-volume and volume-time curves, felt to be significant enough to affect measurement	BOLD QC requirements ATS criteria NIOSH guidelines
Cough that affects measurement	c (cough)	Cough within 1st second which is likely to alter FEV_1, or a later cough which causes early termination.	BOLD QC requirements ATS criteria NIOSH guidelines
Zero flow error	z (zero)	Continuous rise of volume-time curve, with no plateau, and long tail on flow-volume curve, which is felt related to error rather than obstructive impairment	BOLD QC requirements NIOSH guidelines

PEFT: Peak expiratory flow time; BEV: Back extrapolated volume; BOLD: Burden of Obstructive Lung Disease Study; ATS: American Thoracic Society; NIOSH: National Institute for Occupational Safety & Health, Centres for Disease Control & Prevention; QC: Quality Control.

Data were used for a given patient at a given study visit only if 2 usable curves with no errors were available, and if the differences between both the best/next-best FEV_1 and FVC readings between these curves was ≤200ml. Patients with spirometry which did not meet these criteria were defined as having 'missing' data for this study visit.

Spirometry interpretation

Spirometry data meeting these standards were standardised for age, sex and height using the Global Lung Initiative 2012 (GLI-2012) African reference ranges.(3) Data were described using z-scores, and 5% lower limit of normal (LLN) cut-offs used to determine patterns of abnormality (obstruction: FEV_1/FVC ratio <LLN; low FVC: FEV_1/FVC ratio ≥LLN & FVC<LLN; normal: FEV_1/FVC ratio ≥LLN & FVC≥LLN). Reversibility was defined as a >200ml and >12% increase in absolute FEV_1 or FVC following bronchodilator.(4)

Appendix 3: HRCT reporting procedures

Derivation of scoring tool

There exist no validated image scoring tools for the measurement of post-TB lung damage. A novel tool was therefore developed for use here (Table 3). This was informed by a systematic review of the existing literature on post-TB lung damage,(5) pictorial essays of chest imaging at various stages of PTB disease, and review of image scoring systems commonly used in bronchiectasis, COPD, and interstitial lung disease studies. It was developed by the study PI (JM) and two consultant radiologists: a consultant chest radiologist with predominantly UK specialist respiratory experience (JJ), and a UK-based ID radiologist with experience of TB related pathology and imaging in sSA (EJ). Particular attention was paid to the selection of variables used to measure bronchiectasis and airways pathology. Established radiological criteria from the Fleischner guidelines were used throughout,(6) except for the category of 'Emphysematoid destruction' which is a feature described in the TB and interstitial lung disease (ILD) literature only.(7) Joint scoring of a training set of CT images obtained from a previous study of patients receiving TB-retreatment in urban Blantyre was used to refine the scoring tool prior to use.

Image scoring

All HRCT images were independently scored by two consultant radiologists (EJ and JJ). Anonymised images were used, with no accompanying demographic or health related information, and images were provided to both radiologists in the same format and order over the course of the study. CTs were scored on a lobar basis. For scoring purposes the lingula was counted as a separate lobe using the level of the origin of the lingula bronchus to demarcate the boundary of the lingula from the left upper lobe. Scores were entered directly into a live reporting database.

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Data from the first 20 independently reported scans from within this study were openly reviewed by both primary readers together to consolidate training. Re-scoring of initial data for these first 20 scans was permitted following this review, but all subsequent images were independently reported with no comparison or changes allowed.

Table E3: Novel HRCT chest scoring tool, for post-tuberculosis lung damage

Variable	Definition	Lobar level scoring options
PARENCHYMAL VARIABLES	Scored at lobal level. Percentage of parenchyma affected by each pattern estimated to nearest 5%. Lobar percentages summed over whole lung to give total lung score /600.	
Parenchymal bands	Linear opacity 1-3mm thick, up to 5cm long. Usually extends to visceral pleura. May be accompanied by anatomical distortion	% of parenchyma (to nearest 5%)
Atelectasis	Reduced lung volume which may be accompanied by displacement of fissures, bronchi, vessels.	
Consolidation	Homogeneous increase in lung parenchymal attenuation which obscures the margins of vessels and airway walls. An air bronchogram may be present.	
Ground glass opacification	Hazy increased lung opacity with preservation of bronchial and vascular margins	
Mosaicism	Specifically, the low attenuation component of a variable “mosaic” attenuation pattern within the lung	
Emphysema	Focal areas or regions of low attenuation usually without visible walls	
Emphysematoid destruction	Focal area of destruction/emphysematous change associated with features of healing TB, suggesting destruction of acini/small airways.	
Cavities / cystic airspaces	Gas filled structure, seen as a lucency or low-attenuation area within a pulmonary consolidation, a mass, or a nodule. Consolidation may have resolved leaving a thin wall only.	
Normal	Normal parenchyma, not affected by any of the pathological processes above	
BRONCHIECTASIS VARIABLES	Scored at lobar level. Lobar extent and severity scores summed across whole lung to give total score /18.	
Bronchiectasis Airway lumen diameter greater than accompanying pulmonary artery outer diameter, OR Airways visible within 1 cm of the lung periphery, OR Lack of normal airway tapering	Extent (Maximal score of 2 for middle lobes – 2 segments only)	0: Absent 1: ≤1 BP segment 2: 2 BP segments 3: ≥ 3 BP segments
	Pattern (Nominal variable, scored only if bronchiectasis seen and ‘extent’ score >0)	1: Cystic (‘Ballooned' outline, with diameter increasing towards periphery) 2: Cylindrical (Regular and straight outline, with abrupt termination) 3: Varicose (Irregular beaded bronchial outline with bulbous termination)
	Severity Maximum degree of airway dilatation, to be measured by comparing diameter of airway lumen to diameter of adjacent vessel. (Scored only if bronchiectasis seen and ‘extent’ score >0)	1: Trivial (bronchial lumen is <twice adjacent vessel diameter) 2: Bronchial lumen is 2-3 times adjacent vessel diameter 3: Bronchial lumen is >3 times adjacent vessel diameter
AIRWAY VARIABLES	Scored at lobar level. All variables independent of each other. Lobar scores summed across whole lung to give total score /18.	

Bronchial wall thickening	Thickening of bronchial walls	0: Absent 1: Mild 2: Moderate 3: Severe Missing: Unable to assess
Airway plugging	Plugging seen in large airways	0: Absent 1: Mild 2: Moderate 3: Severe
Tree in bud	Centrilobular branching pattern in the peripheral airways, resembling a budding tree.	0: Absent 1: Mild 2: Moderate 3: Severe
CAVITY VARIABLES	Scored at lobar level. Independent of parenchymal scores. Lobar scores combined to give whole-lung data.	
Cavity / cystic airspace Gas filled space, seen as a lucency or low-attenuation area within a pulmonary consolidation, a mass, or a nodule. Consolidation may have resolved leaving a thin wall only.	Extent	0: Absent 1: 1-2 cavities 2: 3-5 cavities 3: >5cavities
	Maximum size (Scored only if bronchiectasis seen and 'extent' score >0)	Maximum diameter (mm)
	Mycetoma Discrete mass of hyphae, within a cavity. May have air crescent sign. May have sponge like pattern with areas of calcification. (Scored only if bronchiectasis seen and 'extent' score >0)	0: Absent 1: Present
OTHER LOBAR VARIABLES	Scored at lobar level, with scores combined to give whole-lung data	
Nodules	Rounded opacities, well or poorly-defined, >5mm, measuring up to 3cm in diameter	0: Absent 1: <5 nodules 2: ≥5 nodules 3: Miliary
WHOLE LUNG VARIABLES	Scored at level of hemithorax / whole lung	
Pleural effusion	Accumulation of fluid within pleural space	0: Absent 1: Present
Pleural thickening	Pleural thickening of ≥10mm	0: Absent 1: Present
Lymph nodes	Mediastinal / hilar lymph nodes ≥10mm diameter	0: Absent 1: Present

Lobar scores generated for each variable were summed across the whole lung, and these whole lung scores were then compared between readers. The Cohen's kappa score (binary variables), weighted Cohen's kappa score with quadratic weighting (ordinal variables with multiple categories), and intra-class correlation coefficients (continuous variables) were calculated to measure inter-reader agreement.

Consensus review of imaging reports

Consensus review was completed for the scans with the most discrepant scores for reported variables (Table 5), with cut-offs specified after review of the primary reporting data. For continuous variables, the most discrepant ~5% of scans for each variable were selected for review: assuming that the difference in scores between readers had a normal distribution, this rule identified scans with differences >2 standard deviations away from the mean difference for each variable, but allowed the absolute magnitude of discrepancy tolerated to vary between variables. Where a variable required review for a particular scan, all lobes in which discrepancy was seen between original readers were reviewed by the consensus reader.

Consensus reading was performed by a third independent chest radiologist (HZ). Reviews were performed at the end of the study, and the consensus reader was provided with both the HRCT images and anonymised original reads from each of the primary radiologists. When reviewing discrepant variables/lobes, the reviewer was able to either choose one of the original scores or generate their own response. For pragmatic reasons, no consensus review was performed for pleural pathology (final readings were taken from one reader only) and lymphadenopathy for which non-contrast imaging is known to have limited sensitivity and which was shown to have very low inter-reader agreement suggesting poor validity of data.

Table E4: Methods used to select scans and variables for consensus review, including the difference in scores used as a cut-off for consensus reading, the number of scans reviewed and the approach underlying this decision given.

Variable group	Variable (Range of possible scores, whole lung level)	Inter-reader consistency for whole-lung variable ICC (95% CI) OR Kappa (SE)	Threshold difference, at which consensus review required	Number of scans for review of ≥1 lobe	Number of lobes for which clean reads available (RUL/RML/RLL – LUL/Lingula/LLL) n (%) of scans with all lobes having clean reads[††]
Parenchymal variables	Atelectasis score (0-600)	ICC: 0.81 (0.77-0.84)	≥60 points	20	R lobes: 308 / 330 / 334 L lobes: 308 / 321 / 332 Clean reads all lobes: 177/385 (46.0%)
	Parenchymal banding score (0-600)	ICC: 0.43 (0.35 -0.51)	≥75 points	22	R: 221/204/232 L: 231 / 244/ 238

					Clean reads all lobes: 86/385 (22.3%)
	Consolidation score (0-600)	ICC: 0.43 (0.34 – 0.51)	≥40 points	18	R 311 / 346 / 338 L: 301 / 338 / 342 Clean reads all lobes: 194/385 (50.4%)
	Ground glass opacification score (0-600)	ICC: 0.49 (0.41 – 0.57)	≥60 points	22	R: 353 / 367 / 366 L: 362/366 / 360 Clean reads all lobes: 292/385 (75.8%)
	Mosaicism score (0-600)	ICC: 0.55 (0.48-0.62)	≥160 points	22	R: 236 / 242/232 L: 234 / 259 / 226 Clean reads all lobes:105/385 (27.3%)
	Emphysema score (0-600)	ICC: 0.50 (0.42 – 0.57)	≥25 points	18	R: 335 / 372/ 364 L: 339 / 375 / 363 Clean reads all lobes:291/385 (75.6%)
	Emphysematoid destruction score (0-600) †	ICC: 0.27 (0.18 – 0.36)	≥15 points	18	R: 379 / 380 / 378 L: 374 / 384 / 371 Clean reads all lobes: 346/385 (89.9%)
	Cavities score (0-600)	ICC: 0.81 (0.77-0.84)	≥25 points	23	R: 344 / 378 / 370 L: 349 / 380 / 375 Clean reads all lobes: 301/385 (78.2%)
	Normal lung score (0-600)	ICC: 0.80 (0.76 – 0.83)	≥170 points	21	R:183 / 161 / 172 L: 196 / 208 /186 Clean reads all lobes: 73/385(19.0%)
Bronchiectasis	Whole lung bronchiectasis extent score (0-16)	Weighted kappa: 0.72 (0.05)	≥6 points	20	R: 296 / 340/ 324 L: 297 / 337 / 321 Clean reads all lobes: 195/385 (50.7%)
	Whole lung bronchiectasis severity score (0-18)	Weighted kappa: 0.66 (0.05)	≥6 points	25	R: 281 / 315 / 299 L: 266 / 307 / 292 Clean reads all lobes: 133/385 (34.6%)
	Whole lung bronchiectasis pattern score (0-18)*	Weighted kappa: 0.67 (0.05)	≥6 points	20	R: 41/78 (52.6%); 7/15 (46.7%); 16/35 (45.7%) L: 42/80 (52.5%); 29/39 (74.4%); 25/39 (64.1%)
	Whole lung presence / absence of bronchiectasis ‡	N/a	All with discrepancy	79	N/a
	Number of lobes affected (0-6) ‡	N/a	≥3 lobes	30	N/a
Cavities / cystic airspaces	Whole lung cavity /cystic airspace extent score (0-18)	Weighted kappa: 0.65 (0.04)	≥4 points	23	R: 359 / 383 / 372 L: 362 / 380 / 371 Clean reads all lobes: 327/385 (84.9%)
	Whole lung presence / absence of cavities or cystic airspaces ‡	N/a	All with discrepancy	58	N/a
	Whole lung presence / absence of mycetoma	Kappa: 0.49 (0.05)	All with discrepancy	10	R: 98/100 (98.0%); 16/16 (100%); 32/32 (100%) L: 103/105 (98.1%); 25/26 (96.2%); 44/44 (100%)
	Maximum cavity size (size in mm)	N/a	≥22mm	20	N/a
	Parenchymal change allocated to cavities/cystic	N/a	≥10% parenchyma in lobe	7	N/a

	airspaces, but no cavities seen, in at least 1 lobe [§]				
	Cavity seen, but no % parenchyma allocated, in at least 1 lobe [§]	N/a	≥10mm cavity seen in lobe	26	N/a
Nodules	Whole lung nodule extent score (0-18)	Weighted kappa: 0.65 (0.05)	≥5	22	R: 267 / 320 / 304 L: 274 / 315/ 291 Clean reads all lobes: 115/385 (29.9%)
Other airway variables	Whole lung tree in bud severity score (0-18)	Weighted kappa: 0.45 (0.04)	≥9	20	R: 217 / 247 / 226 L: 219 / 248 / 225 Clean reads all lobes: 67/385 (17.4%)
	Whole lung airway plugging severity score (0-18)	Weighted kappa: 0.51 (0.05)	≥5	18	R: 284 / 328 / 302 L: 280 / 313 / 313 Clean reads all lobes: 153/385 (39.7%)
	Whole lung bronchial wall thickening severity score (0-18)	Weighted kappa: 0.42 (0.05)	≥8	22	R: 193 / 248 / 228 L: 198 / 226 / 205 Clean reads all lobes: 73/385 (19.0%)
Whole lung variables	Presence /absence of pleural pathology [‖]	Kappa: 0.60 (0.05)	N/a	0	368/385 (95.6%)
	Presence /absence of lymphadenopathy[‖]	Kappa: 0.17 (0.05)	N/a	0	339/385 (88.1%)
All variables	Total number of CT scans requiring consensus review of ≥1 lobe		239 scans		

[†] Term derived from TB imaging literature, and not Fleischner defined.

*Bronchiectasis pattern is an ordinal variable, but lobar scores treated as nominal and summed / compared to identify scans for consensus review only.

[‡] Derived measures of pathology, for which no measures of inter-reader agreement were calculated.

[§] Discrepancies within scoring tool, with differences in the reporting of the extent of cavities / cystic airspaces between sections.

[‖] No consensus review performed: final scores derived from a single reader only (pleural pathology), or data not used given very low levels of inter-reader agreement (lymphadenopathy).

[††]Clean reads: lobes with either identical scores from original readers, or score determined by consensus review

Final dataset development

Original and consensus reads were combined to form a single 'final' dataset. Where there was agreement between original readers for a given variable in a given lobe, this score was used as the final data point. Where original readers had disagreed and a consensus review had been performed, the consensus score was used as the final data point. Where original readers had disagreed, but no consensus read was available, the approach taken varied: scores from the original readers were averaged for continuous variables (eg. parenchymal scores), pathology was considered present if either or both original readers felt it to be so for binary scores (eg. mycetoma, pleural pathology),

and random selection of original reads was used for nominal variables which could not be combined (eg. bronchiectasis pattern).

Lobar scores were summed to generate whole-lung level scores for data analysis. This pragmatic approach assumes that the impact of pathology in all lobes is equal, and that each lobe contributes the same volume of parenchyma / pathology to the overall lung, regardless of variation in their true size. Several new variables were derived including: lobar presence / absence scores for airway pathologies (E.g. moderate to severe bronchiectasis was considered present in a lobe if the final score was ≥2), a composite variable for 'destroyed lobes' (≥90% of parenchyma was occupied by atelectasis, parenchymal banding or destroyed by cavities/cystic airspaces), and a % score for the total amount of abnormal parenchyma seen across the lung both with and without mosaicism.

The data collection team and participants remained blind to imaging results until after the final study visit, at which point written imaging reports were provided to each participant, and findings explained to each individual by a respiratory physician.

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Appendix 4: Sample size calculation

An *a priori* definition of severe PTLD was established prior to data analysis, based on parameters known to predict adverse patient outcomes in other chronic lung diseases (bronchiectasis, COPD, and ILD) and consensus discussion between a panel of respiratory and TB researchers and clinicians[1](Table 5). The prevalence of severe PTLD was estimated at between 10-50%. A sample size of 400 was sufficient to determine the prevalence of severe PTLD within this range with +/-5% precision and 95% confidence.

Table E5: Composite *a priori* definition of PTLD

Criteria	PTLD present
Abnormal spirometry OR	Airway obstruction with FEV1/FVC ratio<LLN & FEV1<LLN OR Low FVC with FEV1/FVC ratio≥0.7 & FVC<LLN
Abnormal CT Imaging	Moderate-severe bronchiectasis in ≥3 lobes OR Parenchymal abnormality of ≥1/3 of the lung tissue, excluding mosaicism

LLN: Lower limit of normal, as classified using GLI-2012 reference ranges.

The rationale for the parameters and cut-offs included in the *a priori* definition are given below. The studies on which these findings are based include data from non-TB populations in high-resource settings, but was felt plausible that similar outcomes may be seen in in the post-TB population in Malawi also.

Spirometry criteria:

Use of the LLN to define abnormal spirometry is widely accepted practice.(3) Reduced FEV_1 volumes predict mortality both amongst those with COPD, and the general population, with causes including respiratory failure and cardiovascular disease.(8) Recent data suggest that the FVC may be an

[1] JM, SBS, PM, Professor Jane Carter (Respiratory physician and Associate Professor of Medicine at Brown University (USA), past-president of The International Union Against Tuberculosis and Lung Disease), Dr Jeremiah Chakaya (Respiratory physician, lead of Kenyan National TB Control Programme, past-president of The International Union Against Tuberculosis and Lung Disease)

additional, or even more important, driver of mortality even in the absence of persistent symptoms or an underlying diagnosis of lung pathology.(9, 10) Both airway obstruction with reduced FEV_1, and small lungs with reduced FVC were therefore included.

Imaging criteria:

Bronchiectasis and parenchymal damage are common features of PTLD.(5) Bronchiectasis affecting ≥3 lobes on CT imaging has been associated with hospital admissions and all-cause mortality in previous bronchiectasis cohort studies.(11, 12) Studies developing prognostic tools for patients with emphysema and scleroderma related ILD suggest that a cut-off of 20-30% abnormal parenchyma can help to differentiate between those at low and moderate risk of mortality.(13, 14) Because the relative importance of each pattern of parenchymal pathology in PTLD is not known, a cumulative variable including all patterns of parenchymal pathology was used in the definition given here. The extent of mosaicism, which reflects gas trapping rather than parenchymal damage, was not included.

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Appendix 5: Comparison of baseline study spirometry data with community data

Table E6: Comparison of the age-stratified prevalence estimates of moderate-severe airway obstruction and spirometric restriction within this study cohort, with survey weighted prevalence estimates from the 2013-2014 BOLD study in urban Blantyre.(15) All data standardised using NHANES III Caucasian reference ranges.

Age group (n at baseline/ 1-year)	Mod-severe obstruction FEV/FVC<0.7 and FEV1<80% predicted			Low FVC FEV1/FVC>=0.7 and FVC<80% predicted		
	Post-TB cohort TB Rx completion % (SE)	Post-TB cohort 1-year f'up % (SE)	BOLD data set % (SE)	Post-TB cohort TB Rx completion % (SE)	Post-TB cohort 1-year f'up % (SE)	BOLD data set % (SE)
15-19yrs (n=17/13)	11.8% (7.8%)	15.4% (10.0%)	-	82.4% (9.2%)	61.5% (13.5%)	-
20-29yrs (n=83/77)	4.8% (2.4%)	6.5% (2.8%)	2.4% (1.0%)	71.1% (5.0%)	64.9% (5.4%)	32.7% (4.0%)
30-39yrs (n=160/147)	7.5% (2.1%)	8.8% (2.3%)	2.9% (1.5%)	64.4% (3.8%)	55.8% (4.1%)	42.0% (3.8%)
40-49yrs (n=79/75)	11.4% (3.6%)	16.0% (4.2%)	2.3% (0.9%)	62.0% (5.5%)	41.3% (5.7%)	28.3% (4.4%)
50-59yrs (n=17/15)	11.8% (7.8%)	13.3% (8.8%)	9.8% (2.8%)	17.6% (9.2%)	6.7% (6.4%)	39.4% (6.6%)
60+yrs (n=9/9)	11.1% (10.5%)	33.3% (15.7%)	12.0% (4.4%)	33.3% (15.7%)	33.3% (15.7%)	13.8% (6.4%)

Appendix 6: Clinical and respiratory parameters, stratified by HIV-status

Table E7: Clinical and respiratory parameters measured at TB treatment completion, 6-month and 12-month study visits, stratified by HIV-status [§] (n=403)

Parameter	TB treatment completion			6-month visit			12-month visit		
	HIV-negative (n=159)	HIV-positive (n=244)	p-value	HIV-negative (n=143)	HIV-positive (n=231)	p-value	HIV-negative (n=142)	HIV-positive (n=225)	p-value
Symptom prevalence (n, %) [†]									
Breathlessness									
- Never/only with chest infections	83 (52.2%)	143 (58.6%)	0.069	96 (67.1%)	186 (80.5%)	0.014*	101 (71.1%)	181 (80.4%)	0.086
- Few days per month	65 (40.9%)	95 (38.9%)		40 (28.0%)	38 (16.5%)		35 (24.7%)	40 (17.8%)	
- ≥Several days per week	11 (6.9%)	6 (2.5%)		7 (4.9%)	7 (3.0%)		6 (4.2%)	4 (1.8%)	
Cough									
- Never/only with chest infections	86 (54.1%)	172 (70.5%)	0.002*	106 (74.1%)	177 (76.6%)	0.860	113 (79.6%)	194 (86.2%)	0.233
- Few days per month	66 (41.5%)	68 (27.9%)		31 (21.7%)	45 (19.5%)		26 (18.3%)	27 (12.0%)	
- ≥Several days per week	7 (4.4%)	4 (1.6%)		6 (4.2%)	9 (3.9%)		3 (2.1%)	4 (1.8%)	
Sputum production									
- Never/only with chest infections	109 (68.6%)	190 (77.9%)	0.077	113 (79.0%)	186 (80.5%)	0.940	118 (83.1%)	200 (88.9%)	0.240
- Few days per month	45 (28.3%)	51 (20.9%)		28 (19.6%)	42 (18.2%)		23 (16.2%)	23 (10.2%)	
- ≥Several days per week	5 (3.1%)	3 (1.2%)		2 (1.4%)	3 (1.3%)		1 (0.7%)	2 (0.9%)	
Wheeze									0.235
- Never/only with chest infections	147 (92.5%)	223 (91.4%)	0.823	130 (90.9%)	215 (93.1%)	0.188	134 (94.4%)	218 (96.9%)	
- Few days per month	11 (6.9%)	18 (7.4%)		11 (7.8%)	16 (6.9%)		8 (5.6%)	7 (3.1%)	
- ≥Several days per week	1 (0.6%)	3 (1.2%0		2 (1.4%)	0 (0 %)		0 (0%)	0 (0%)	
Any respiratory symptom, ≥monthly	103 (64.8%)	142 (58.2%)	0.186	62 (43.4%)	75 (32.5%)	0.034*	55 (38.7%)	57 (25.3%)	0.007*
Symptom impact (n, %)									
Self-reported impact of chest on activities									
- Does not stop any activities	77 (48.4%)	122 (50.0%)	0.837	108 (75.5%)	181 (78.4%)	0.578	108 (76.1%)	187 (82.1%)	0.241
- Prevents 1-2 activities	67 (42.1%)	97 (39.8%)		27 (28.9%)	41 (17.8%)		28 (19.7%)	28 (12.4%)	
- Prevents most / all activities	15 (9.4%)	25 (0.10%)		8 (5.6%)	9 (3.9%)		6 (4.2%)	10 (4.4%)	
Self-reported impact of chest on work									
- Does not affect work	95 (59.8%)	146 (59.8%)	0.964	115 (80.4%))	192 (83.1%)	0.797	122 (85.9%)	200 (88.9%)	0.022
- Interferes with / made me change work	58 (36.5%)	90 (36.9%)		24 (16.8%)	33 (14.3%0		20 (14.1%)	18 (8.0%)	
- Made me stop work	6 (3.8%)	8 (3.3%)		4 (2.8%)	6 (2.6%)		0 (0%)	7 (3.1%)	
Breathless at rest / during personal care	0 (0%)	2 (0.8%)	0.253	1 (0.7%)	1 (0.4%)	0.731	1 (0.7%)	1 (0.4%)	0.742
Walks slower than peers / stops for rest at own pace	45 (28.5%)	62 (25.5%)	0.512	26 (18.2%)	31 (13.4%)	0.213	28 (19.7%)	35 (15.6%)	0.303
Breathless on hills	79 (50.0%)	96 (39.5%)	0.038*	42 (29.4%)	39 (16.9%)	0.004*	40 (28.2%)	42 (18.9%)	0.033*
Quality of life									
Self-reported general health (n, %)									
- Poor/fair	45 (28.3%)	70 (28.7%)	0.933	23 (16.1%)	30 (13.0%)	0.404	9 (6.3%)	13 (5.8%)	0.826
- Good/excellent	114 (71.7%)	174 (71.3%)		120 (83.9%)	201 (87.0%)		133 (93.7%)	212 (94.2%)	
SGRQ Total score (median, IQR)	10.3 (1.8 – 24.7)	8.2 (0.9 – 22.4)	0.1135	1.1 (0.4 – 16.4)	0.4 (0.0 – 7.3)	0.1043	0.4 (0 – 11.6)	0.4 (0 – 4.6)	0.1300
SGRQ Symptom score (median, IQR)	13.7 (2.7 – 28.8)	10.3 (2.7 – 21.8)	0.0185*	2.7 (0 – 21.9)	2.7 (0 – 10.7)	0.0991	2.7 (0 – 21.4)	2.7 (0 – 10.3)	0.1204

SGRQ Activity score (median, IQR)	12.2 (0 – 41.4)	11.2 (0 – 35.2)	0.1212	0 (0 – 24.1)	0 (0 – 11.2)	0.0279*	0 (0 - 18.2)	0 (0 – 0)	0.0994
SGRQ Impact score (median, IQR)	7.3 (0 – 15.5)	5.5 (0 – 15.0)	0.2777	0 (0 – 7.3)	0 (0 – 5.6)	0.1411	0 (0 – 5.6)	0 (0 – 1.6)	0.0214*
Clinical observations									
BMI (kg/m^2) (median, IQR)	20.3 (18.8 – 21.7)	20.7 (19.0 – 22.6)	0.0471*	20.5 (19.0 – 22.1)	21.2 (19.6 – 23.3)	0.0055*	20.7 (19.2 – 22.5)	21.5 (19.6 – 23.8)	0.0060*
Oxygen saturations (%) (median, IQR)	98 (97 – 99)	98 (98-99)	0.0042*	98 (97-98)	98 (97 – 99)	0.0327*	98 (97-98)	98 (97 – 98)	0.2691
Hypoxaemia (sats <92%) (n, %)	4 (2.5%)	2 (0.8%0	0.169	4 (2.8%)	2 (0.9%)	0.149	3 (2.1%)	1 (0.4%)	0.134
Respiratory rate (breaths/minute) (median, IQR)	19 (17 – 20)	18 (17 – 20)	0.9749	19 (18 – 21)	19 (18 – 21)	0.3201	20 (19 – 22)	20 (19 – 22)	0.8404
Heart rate (beats/minute) (median, IQR)	73 (64 – 86)	82 (72 – 91)	0.0000*	73 (65 – 86)	77 (69 – 86)	0.0117*	73 (6 3- 84)	78 (70 – 87)	0.0004*
Pedal oedema (n, %)	1 (0.6%)	6 (2.5)	0.169	1 (0.7%)	2 (0.9%)	0.861	0 (0%)	3 (1.3%)	0.167
Palatal Kaposi Sarcoma (n=368) (n, %)	2 (1.4%)	6 (2.7%)	0.418	1 (0.7%)	9 (3.9%)	0.063	0 (0.0%)	1 (0.4%)	0.426
Blood tests									
Haemoglobin (g/dL) (median, IQR)	14.6 (13.3 – 15.6)	13.1 (11.7 – 14.5)	0.0000*						
Positive aspergillus IgG ELISA	1 (0.6%)	2 (0.8%)	0.828				0 (0%)	2 (0.8%)	0.252
6-minute walk test (n=395 / 355)									
Distance (m) (mean, sd)	576 (524 – 627)	570 (508 – 617)	0.3360				624 (576 – 663)	606 (564 – 654)	0.1149
Spirometry (n=365 / 341 / 336) ‡									
FEV_1 z-score (mean, sd)	-1.27 (1.33)	-0.94 (1.19)	0.0146*	-1.17 (1.33)	-0.74 (1.17)	0.0019*	-1.15 (1.28)	-0.70 (1.10)	0.0007*
FVC z-score (mean, sd)	-1.08 (1.29)	-0.80 (1.18)	0.0374*	-0.92 (1.29)	-0.50 (1.10)	0.0013*	-0.86 (1.16)	-0.44 (1.02)	0.0006*
FEV_1/FVC ratio z-score (mean, sd)	-0.47 (1.40)	-0.32 (1.15)	0.2492	-0.54 (1.49)	-0.49 (1.14)	0.7310	-0.62 (1.45)	-0.49 (1.19)	0.3728
Pattern of spirometry - Obstruction (FEV1/FVC ratio <LLN) - Low FVC (FEV1/FVCratio≥LLN & FVC<LLN) - Normal (FEV1/FVC ratio ≥LLN & FVC≥LLN)	 27 (19.0%) 36 (25.4%) 79 (55.6%)	 25 (11.3%) 37 (16.7%) 159 (72.0%)	 0.006*	 29 (22.7%) 23 (18.0%) 76 (59.4%)	 31 (14.6%) 22 (10.4%) 159 (75.0%)	 0.010*	 28 (21.9%) 23 (18.0%) 77 (60.2%)	 31 (15.0%) 20 (9.7%) 156 (75.4%)	 0.011*
CXR findings (n=403 / 361)									
% Abnormal parenchyma (median, IQR)	4.6 (0.8 – 13.3)	1.7 (0 – 7.9)	0.0000*				4.0 (0.8 – 10.8)	1.0 (0.0 – 5.0)	0.0000*
Ring and tramline severity score (0-18) (median, IQR)	2.0 (0.0 – 3.5)	0.5 (0.0 – 2.5)	0.0005*				1.5 (0.0 – 3.0)	0.5 (0.0 – 2.0)	0.0065*

*Statistically significant difference between HIV-positive and negative groups, at p<0.05 level.

†Symptom questions derived from SGRQ: Over the past 3-months I have (had shortness of breath / coughed / brought up sputum / had attacks of wheezing): not at all / only with chest infections / a few days a month / several days a week / most days a week; If you have tried to work in the past 3-months: my chest trouble does not affect my work / my chest trouble interferes with my work or made me change my work / my chest trouble made me stop work; Which of these statements best describes how your chest affects you: It does not stop me doing anything I would like to do / It stops me doing 1-2 things I would like to do / it stops me doing most of the things I would like to do / It stops me doing everything I would like to do.

‡ BOLD standard data available for n=365/405 at baseline, n=341/376 at 6-months, and n=336/368 at 12-month study visits. Data age / sex / height standardised using GLI 2012 African American reference ranges to generate z-scores.

§ Data compared between HIV groups using Chi^2 for categorical, and Student's t-test / Wilcoxon rank sum for continuous variables.

Appendix 7: CT imaging data, stratified by HIV-status

Table E8: Final CT imaging data, generated from original and consensus reads, stratified by HIV status (n=383 individuals)

Pathology	All scans (n=385) Median (IQR) [Full range], or N (%)	HIV-negative (n=148) Median (IQR) [Full range] or N (%)	HIV-positive (n=235) Median (IQR) [Full range] or N (%)	p-value
% parenchymal pathology , whole lung level				
Atelectasis and banding	7.5 (2.9 – 14.2) [0.0 – 53.3]	9.2 (5.8 – 17.5) [0.0 – 53.5]	5.8 (2.5 – 11.7) [0.0 – 43.3]	0.0000*
Cavities / cystic air spaces	0.0 (0.0 – 1.7) [0.0 – 46.7]	0.8 (0.0 – 2.7) [0.0 – 46.7]	0.0 (0.0 – 0.8) [0.0 – 27.5]	0.0001*
Mosaicism	5.4 (0.8 – 14.2) [0.0 – 54.2]	6.7 (2.1 – 15.2) [0.0 – 42.1]	4.6 (0.4 –12.5) [0.0 – 54.2]	0.0240*
Emphysema	0.0 (0.0 – 0.8) [0.0 – 71.7]	0.0 (0.0 – 0.4) [0.0 – 64.2]	0.0 (0.0 – 0.8) [0.0 – 71.7]	0.0161*
Ground glass	0.0 (0.0 – 0.8) [0.0 – 45.0]	0.0 (0.0 – 0.8) [0.0 – 27.5]	0.0 (0.0 – 0.8) [0.0 – 45.0]	0.2759
Consolidation	0.8 (0.0 – 2.1) [0.0 – 18.3]	0.8 (0.0 – 2.1) [0.0 – 18.3]	0.8 (0.0 – 2.1) [0.0 – 12.5]	0.1279
Emphysematous destruction	0.0 (0.0 – 0.4) [0.0 – 27.5]	0.0 (0.0 – 0.8) [0.0 – 20.0]	0.0 (0.0 – 0.4) [0.0 – 27.5]	0.1186
Total abnormal parenchyma, any pattern	22.9 (9.2 – 39.2) [0.0 – 100.0]	30.0 (13.5 –41.0) [0.0 – 100.0]	18.3 (6.7– 37.9) [0.0 – 95.8]	0.0003*
Total abnormal parenchyma, excluding mosaicism[†]	12.1 (5.0 – 25.0) [0.0 – 100.0]	15.6 (7.9 – 30.0) [0 – 100.0]	10.0 (3.8 – 21.7) [0 – 90.0]	0.0003*
Number of 'destroyed' lobes [‡] - 0 - 1-2 - 3	 349 (90.7%) 33 (8.6%) 3 (0.8%)	 126 (85.1%) 19 (12.8%) 3 (2.0%)	 222 (94.5%) 13 (5.5%) 0 (0%)	0.009*
Airway scores, whole lung level				
Bronchiectasis extent score (0-16)	2.5 (0.5 – 4.5) [0.0 – 15.5]	3.0 (2.0 – 5.5) [0 – 15.5]	1.5 (0.0 – 4.) [0.0 – 13.5]	0.0000*
Bronchiectasis severity score (0-18)	2.5 (0.5 – 5.0) [0.0 – 15.5]	3.5 (1.5 – 6.0) [0.0 – 15.5]	2.0 (0.0 – 4.0) [0.0 – 14.5]	0.0000*
Bronchial wall thickening severity score (0-18) (n=327) [§]	3.0 (1.5 – 5.5) [0.0 – 14.5]	3.0 (1.5 – 5.5) [0.0 – 13.5]	3.0 (1.0 – 6.0) [0.0 – 14.5]	0.3883
Tree in bud severity score (0-18)	3.5 (1.5 – 6.0) [0.0 – 17.0]	4.5 (2.5 – 6.5) [0.0 – 14.5]	3.0 (1.0 – 6.0) [0.0 – 17.0]	0.0006*
Airway plugging severity score (0-18)	1.0 (0.0 – 2.0) [0.0 – 12.0]	1.0 (0.5 – 2.5) [0.0 – 9.0]	1.0 (0.0 – 2.0) [0.0 – 12.0]	0.0196*
Number of lobes with moderate – severe bronchiectasis ** - 0 - 1-2 - ≥3	 215 (55.8%0 141 (36.6%) 29 (7.5%)	 65 (43.9%) 71 (48.0%) 12 (8.1%)	 149 (63.4%) 69 (29.4%) 17 (7.2%)	0.001*
Any moderate – severe cystic bronchiectasis [††]	49 (12.7%)	28 (18.9%)	20 (8.5%)	0.0030*
Other variables, whole lung level [‡‡]				
Mycetoma present	5 (1.3%) [§§]	4 (2.7%)	1 (0.4%)	0.0560
Nodules present	228 (59.2%)	88 (59.5%)	139 (59.2%)	0.1540
Pleural pathology (effusions or thickening) present	31 (8.1%)	12 (8.1%)	19 (8.1%)	0.9940

*Statistically significant difference between HIV-positive and negative groups, at p<0.05 level.

[†]Mosaicism excluded as represents areas with gas trapping or impaired perfusion rather than primary parenchymal pathology, and can be observed in 'normal' health adults.

[‡] Destroyed lobe: lobe with ≥90% of parenchyma is occupied by banding, atelectasis, or cavities / cystic airspaces.

§ Data missing where extensive parenchymal pathology in ≥1 lobe prevented evaluation of bronchial wall thickness – those with missing data had more abnormal parenchyma (median 46.3% vs. 18.8% in th, p<0.001) and a lower prevalence of HIV-infection (35.9% vs. 54.0%, p=0.004) compared to those with data for this variable.

** Present if average lobar severity score between two readers, or consensus score, was ≥2, so on average bronchial lumen considered to be 2-3 times adjacent vessel diameter in these lobes.

†† Present if moderate to severe bronchiectasis seen in at least 1 lobe, and pattern here deemed to be cystic based on initial agreement between readers or consensus review of scans, or random selection of initial reader reports where disagreement seen and no consensus review available.

‡‡Mycetoma / nodules present if confirmed by both original readers or the consensus scorer. Pleural pathology present if reported by either original reader.

§§ All patients with mycetoma had negative aspergillus IgG at TB treatment completion.

Appendix 8: Relationship between symptoms and spirometry and imaging findings, at TB treatment completion

Table E9: Relationship between spirometry and CT parameters, and symptoms and quality of life at TB treatment completion with p-values for association

Symptom / QoL Parameter	Prevalence (n, %)	Spirometry parameters (n=365)			CT imaging parameters (median, IQR) (n=385)		
		FEV_1 z-score (mean, SD)*	FVC z-score (mean, SD)*	FEV_1/FVC ratio z-score (mean, SD)*	Bronchiectasis severity score (0-18) (median, IQR)†	% abnormal parenchyma (median, IQR) †	Presence of ≥1 destroyed lobe (n, %, 95% CI)‡
Breathlessness							
- Never/only with chest infections	227 (56.0%)	-0.86 (1.18)	-0.72(1.17)	-0.31 (1.09)	2.5 (1.0 – 4.5)	21.9 (9.2 – 35.4)	16 (7.3%) (4.3 -11.6%)
- ≥ Few days per month	178 (44.0%)	-1.32 (1.31)	-1.14 (1.27)	-0.45 (1.44)	2.5 (0.5 – 5.5)	27.1 (9.6 – 42.9)	20 (12.0%) (7.5 -17.9%)
		p<0.001	p=0.001	p=0.287	p=0.440	p=0.070	p=0.051
Cough							
- Never/only with chest infections	259 (64.0%)	-0.94 (1.22)	-0.84 (1.18)	-0.24 (1.23)	2.0 (0.5 – 4.5)	18.8 (7.1 – 35.0)	13 (5.3%) (2.9-8.9%)
- ≥ Few days per month	146 (36.0%)	-1.27 (1.30)	-1.02 (1.31)	-0.61 (0.11)	3.0 (1.0 – 5.5)	31.3 (12.9 – 48.3)	23 (16.4%) (10.7-23.6%)
		p=0.015	p=0.176	p=0.006	p=0.014	P<0.001	p<0.001
Sputum production							
- Never/only with chest infections	300 (74.1%)	-1.01 (1.23)	-0.89 (1.19)	-0.26 (1.26)	2.0 (0.5 – 4.50)	20.8 (8.3 – 38.8)	24 (8.4%) (5.5-12.3%)
- ≥ Few days per month	105 (25.9%)	-1.22 (1.33)	-0.94 (1.34)	-0.68 (0.12)	2.5 (1.0 – 5.25)	28.1 (13.5 – 42.5)	12 (12.0%) (6.4-20.0%)
		p=0.156	p=0.728	p=0.005	p=0.089	p=0.009	p=0.558
Wheeze							
- Never/only with chest infections	372 (91.8%)	-1.05 (1.26)	-0.92 (1.20)	-0.33 (1.22)	2.5 (0.5 – 5.0)	24.2 (9.2 – 39.6)	34 (9.6%) (6.7-13.1%)
- ≥ Few days per month	33 (8.2%)	-1.23 (1.33)	-0.72 (0.30)	-0.88 (0.29)	2.0 (0.5 – 3.0)	20.4 (9.6 – 38.8)	2 (6.7%) (0.8-22.1%)
		p=0.451	p=0.4071	p=0.0260	p=0.220	p=0.850	p=0.599
Any respiratory symptom							
- Never/only with chest infections	159 (39.3%)	-0.79 (1.19)	-0.68 (1.17)	-0.25 (1.12)	2.0 (0.5 – 4.0)	18.3 (7.1 – 34.6)	7 (4.6%) (1.9-9.3%)
- ≥ Few days per month	246 (60.7%)	-1.23 (1.28)	-1.05 (1.25)	-0.45 (1.34)	2.5 (0.5 – 5.0)	27.3 (10.0-42.9)	29 (12.4%) (8.5-17.3%)
		p=0.001	p=0.013	p=0.130	p=0.349	p=0.002	p=0.011

*Student's t-test; †Wilcoxen rank sum test; ‡Chi-square test

Appendix 9: Multi-level linear regression models for change in spirometry over time

Table E10: Multi-level linear regression, to investigate parameters predicting spirometry values in the first year after TB treatment completion[†] (n=347).[‡]

Variable measured at TB treatment completion	Univariate (ml, 95% CI)	Multivariate, partial model (ml, 95% CI)	Multivariate, full model (ml, 95% CI)
Absolute FEV_1 (ml) over follow-up period			
Time from TB treatment end [§]			
6-months	66.70 (47.39 – 86.01)*	62.17 (41.78 – 82.56)*	65.30 (45.00 – 85.61)*
12-months	72.73 (48.26 – 97.19)*	65.57 (39.47 – 91.68)*	70.56 (44.58 – 96.54)*
HIV positive status	197.57 (83.03 – 312.11)*	193.75 (79.43 – 308.08)*	98.61 (-2.01 – 199.22)
Microbiologically proven TB	-61.81 (-194.79 – 71.17)	-9.12 (-140.23 – 121.99)	30.82 (-84.35 – 145.98)
BMI (kg/m2)	18.32 (9.26 – 27.38)*	7.39 (-1.96 – 16.74)	2.20 (-7.01 – 11.40)
Pack-year smoking history	-7.90 (-20.00 – 4.20)	-4.90 (-16.79 – 7.00)	-0.75 (-11.15 – 9.65)
Maximum education ≤ 1ry school	-108.59 (-225.94 – 8.76)	-108.26 (-224.69 – 8.18)	-37.49 (-139.97 – 64.99)
Respiratory symptoms ≥monthly	-198.98 (-310.07 - -87.90)*		-111.26 (-208.10 - -14.43)*
Bronchiectasis severity score (0-18) – 3-point increments [‖]	-221.04 (-270.18 - -171.91)		-95.56 (-155.64 - -35.47)*
Abnormal parenchyma (%) – 10% increments **	-152.87 (-180.38 - -125.36)		-106.40 (-141.38 - -71.4)*
Variance components (% of model variance): change over time		*1.85%*	*2.53%*
Variance components (% of model variance): baseline FEV1		*94.22%*	*92.05%*
Absolute FVC (ml) over follow-up period			
Time from TB treatment end §			
- 6-months	124.49 (100.70 – 148.30)*	111.77 (87.04 – 136.50)*	115.38 (90.72 – 140.05)*
- 12-months	145.63 (117.66 – 173.59)*	125.21 (95.26 – 155.16)*	131.28 (101.41 – 161.15)*
HIV positive status	197.30 (75.42 – 319.18)*	184.22 (64.02 – 304.43)*	92.94 (-18.17 – 204.04)
Microbiologically proven TB	-18.24 (-159.57 – 123.09)	30.45 (-107.28 – 168.17)	65.99 (-61.11 – 193.09)
BMI (kg/m2)	40.58 (29.97 – 51.19)*	21.34 (10.73 – 31.94)*	15.35 (4.75 – 25.95)*
Pack-year smoking history	-6.04 (-18.88 – 6.81)	-4.38 (-16.86 – 8.10)	-1.87 (-13.34 – 9.59)
Maximum education ≤ 1ry school	-1.34 (-126.72 – 124.04)	-2.97 (-125.46 – 199.51)	63.45 (-49.78 – 176.68)
Respiratory symptoms ≥monthly	-200.30 (-318.52 - -82.08)*		-123.61 (-230.53 - -16.69)*
Bronchiectasis severity score (0-18) – 3-point increments [‖]	-217.87 (-271.12 - -164.62)*		-133.62 (-200.01 - -67.23)*
Abnormal parenchyma (%) – 10% increments **	-131.74 (-162.76 - -100.73)*		-67.03 (-105.67 - -28.39)*
Variance components (% of model variance): change over time		*1.60%*	*2.01%*
Variance components (% of model variance): baseline FVC		*93.18%*	*91.26%*

* OR statistically significant at p<0.05 level.

[†] Model construction based on apriori selection of risk-factors / confounders, and elimination of co-linear variables. Interactions with time evaluated. All univariate & multivariate models coefficients represent the average change in FEV1 or FVC (ml) expected for a 1-unit change in the predictor, holding all other parameters still, and include adjustment for participant age (years), sex, and height (cm).

‡ Participants excluded if absent HIV status at TB treatment completion (n=2), no valid baseline spirometry (n=36), no baseline HRCT imaging (n=20). Includes participants contributing either 6-month (n=13) or 12-month (n=322) follow-up.

§ Negative correlation identified between FEV1 and time (partial model: -0.46 (-0.58 - -0.31) / full model: -0.37 (-0.51 - -0.21)) and FVC and time (partial model: -0.56 (-0.68 - -0.40)/ full model: -0.44 (-0.59 - -0.26)) in all models.

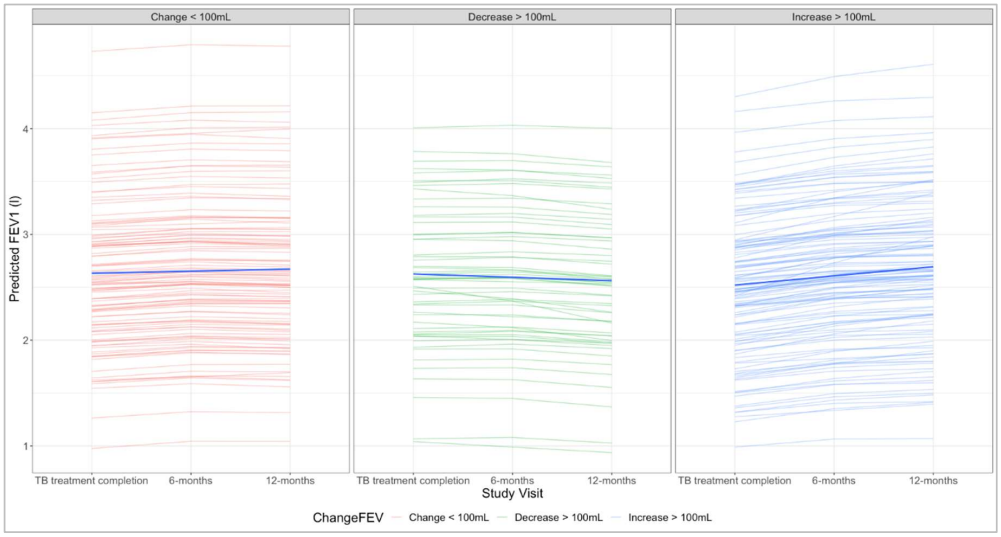
‖ Bronchiectasis severity score (0-18): unweighted sum of 6x lobar bronchiectasis scores ranging from 0 (no bronchiectasis) to 3 (severe dilatation >3 times diameter of adjacent vessel), such that increment of 3 points represents one additional lobe with severe airway dilatation, or combination of 1-3 lobes with less severe disease.

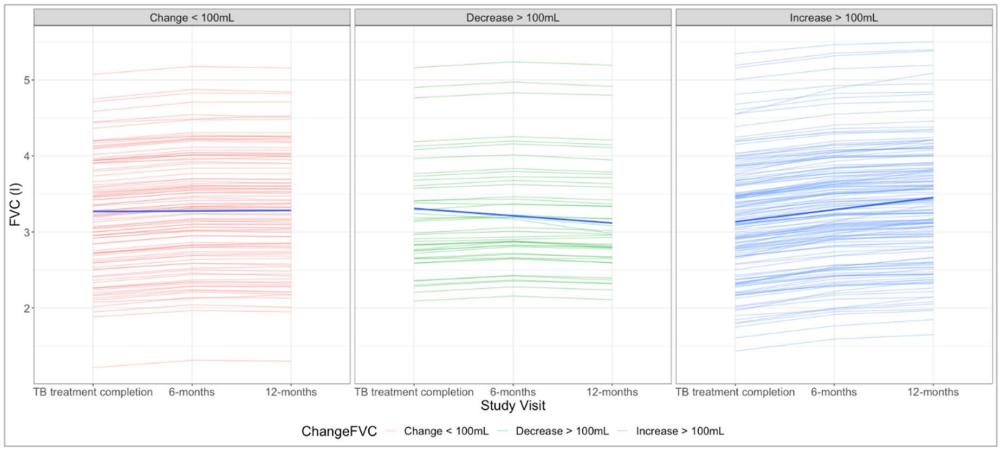
** Total % of parenchymal abnormalities across lung, including: parenchymal banding, atelectasis, consolidation, ground glass change, emphysema, emphysematoid destruction, cavities / cystic airspaces. Excluding mosaicism which represents airway/vascular rather than lung tissue abnormality.

Appendix 10: Predicted change in Spirometry over time

Figure E3: Predicted FEV_1 and FVC volumes at TB treatment completion, and trajectories of change over 1-year, derived from multi-level linear regression models and controlling for patient characteristics, baseline symptoms, and baseline structural lung pathology.

Stratification according to observed change relative to the minimally important clinical difference (MCID) of 100ml.





Appendix 11: Factors predicting chronic respiratory symptoms at 1-year, including sensitivity analyses

Table E11: Logistic regression models of baseline parameters associated with the presence of chronic respiratory symptoms[†] at 1-year (n=325)[‡].

Variables measured at TB treatment end	Univariate, OR (95% CI)	Multivariate, controlling for baseline FEV_1[§] OR (95% CI)	Multivariate, controlling for baseline FVC [§] OR (95% CI)
Age (yrs)	0.99 (0.97 – 1.02)	0.98 (0.95 – 1.01)	0.99 (0.96 – 1.01)
Female sex	1.64 (1.00 – 2.70)*	0.63 (0.27 – 1.46)	0.73 (0.31 – 1.71)
Height (cm)	0.96 (0.93 – 0.99)*	0.98 (0.94 – 1.03)	0.97 (0.93 – 1.02)
HIV status - Negative - Positive, CD4≥200 - Positive, CD4<200	 1.0 0.46 (0.26 – 0.79)* 0.53 (0.29 – 0.98)*	 1.0 0.33 (0.18 – 0.63)* 0.40 (0.19 – 0.84)*	 1.0 0.33 (0.18 – 0.62)* 0.38 (0.18 – 0.80)*
Microbiologically proven TB	0.80 (0.46 – 1.40)	0.74 (0.40 – 1.39)	0.74 (0.40 – 1.38)
BMI (kg/m2)	1.01 (0.93 – 1.10)	1.08 (0.98 – 1.19)	1.08 (0.98 – 1.19)
Hb (g/dL)	0.88 (0.78 – 0.995)*	0.82 (0.70 – 0.98)*	0.82 (0.70 – 0.98)*
Pack-year smoking history	0.98 (0.93 – 1.04)	0.98 (0.93 – 1.04)	0.98 (0.93 – 1.04)
Maximum education ≤ 1ry school	1.28 (0.79 – 2.06)	1.18 (0.67 – 2.08)	1.24 (0.71 – 2.17)
Respiratory symptoms ≥monthly	2.74 (1.62 – 4.64)*	2.42 (1.37 – 4.27)*	2.45 (1.39 – 4.32)*
Absolute FEV1 (100 ml increments)	0.93 (0.89 – 0.96)*	0.95 (0.89 – 1.00)	
Absolute FVC (100 ml increments)	0.95 (0.92 – 0.98)*		0.98 (0.93 – 1.03)
Bronchiectasis severity score (3-point increments, 0-6) [‖]	1.08 (0.86 – 1.36)	0.88 (0.63– 1.22)	0.89 (0.64 – 1.25)
Abnormal parenchyma (10% increments) [††]	1.14 (1.01 – 1.31)*	1.11 (0.91 – 1.35)	1.16 (0.96 – 1.40)

*OR statistically significant at p<0.05 level.

[†]Cough, breathlessness, sputum production, or wheeze with frequency ≥few days/month.

[‡]Participants excluded if absent HIV status at TB treatment completion (n=2), no valid baseline spirometry (n=36), no baseline HRCT imaging (n=20), or no symptom data available at 12-month study visit (n=22).

[§]Co-linearity of FEV_1 and FVC precludes inclusion of both in a single model – separate models constructed to control for baseline level of each.

[‖]Bronchiectasis severity score (0-18): unweighted sum of 6x lobar bronchiectasis scores ranging from 0 (no bronchiectasis) to 3 (severe dilatation >3 times diameter of adjacent vessel), such that increment of 3 points represents one additional lobe with severe airway dilatation, or combination of 1-3 lobes with less severe disease.

[††]Total % of parenchymal abnormalities across lung, including: parenchymal banding, atelectasis, consolidation, ground glass change, emphysema, emphysematoid destruction, cavities / cystic airspaces. Excluding mosaicism which represents airway/vascular rather than lung tissue abnormality.

Table E12: Sensitivity analyses of logistic regression models of baseline parameters associated with the presence of chronic respiratory symptoms † at 1-year (n=347) ‡, with outcomes for those lost to follow-up allocated as positive or negative.

'All symptomatic' models: All participants with missing 1-year symptom data assumed to have ongoing respiratory symptoms (n=22)

'None symptomatic' models: All participants with missing 1-year data assumed to have no ongoing respiratory symptoms (n=22)

Variables measured at TB treatment end	Multivariate model, with FEV_1		Multivariate model, with FVC	
	All symptomatic	None symptomatic	All symptomatic	None symptomatic
Age (yrs)	0.98 (0.95 – 1.01)	0.99 (0.96 – 1.02)	0.98 (0.96 – 1.01)	0.99 (0.97 – 1.02)
Female sex	0.75 (0.34 – 1.65)	0.69 (0.30 – 1.56)	0.87 (0.39 – 1.94)	0.77 (0.34 – 1.76)
Height (cm)	1.00 (0.96 – 1.04)	0.98 (0.93 – 1.02)	0.99 (0.95 – 1.03)	0.97 (0.93 – 1.01)
HIV status - Negative - Positive, CD4≥200 - Positive, CD4<200	 1.0 0.32 (0.18 – 0.59)* 0.50 (0.25 – 1.00)	 1.0 0.39 (0.21 – 0.72)* 0.41 (0.20 – 0.84)*	 1.0 0.32 (0.17 – 0.58)* 0.48 (0.24 – 0.96)*	 1.0 0.38 (0.21 – 0.71)* 0.39 (0.19 – 0.80)*
Microbiologically proven TB	0.79 (0.44 – 1.43)	0.75 (0.41 – 1.39)	0.79 (0.44 – 1.42)	0.75 (0.41 – 1.38)
BMI (kg/m2)	1.07 (0.98 – 1.17)	1.08 (0.98 – 1.18)	1.06 (0.97 – 1.17)	1.07 (0.97 – 1.18)
Hb (g/dL)	0.82 (0.70 – 0.96)*	0.88 (0.75 – 1.03)	0.81 (0.70 – 0.95)*	0.88 (0.75 – 1.03)
Pack-year smoking history	0.97 (0.92 – 1.03)	0.99 (0.93 – 1.04)	0.97 (0.92 – 1.03)	0.99 (0.93 – 1.04)
Maximum education ≤ 1ry school	1.07 (0.63 – 1.81)	1.16 (0.67 – 2.00)	1.11 (0.66 – 1.87)	1.21 (0.70 – 2.07)
Respiratory symptoms ≥monthly	2.49 (1.46 – 4.23)*	2.15 (1.23 – 3.75)*	2.54 (1.50 – 4.31)*	2.19 (1.25 – 3.81)*
Absolute FEV1 (100 ml increments)	0.95 (0.90 – 1.00)*	0.96 (0.90 – 1.01)		
Absolute FVC (100 ml increments)			0.99 (0.94 – 1.04)	0.98 (0.94 – 1.03)
Bronchiectasis severity score (3 point increments, 0-6) §	0.84 (0.61 – 1.15)	0.92 (0.66 – 1.27)	0.86 (0.62 – 1.18)	0.93 (0.67 – 1.29)
Abnormal parenchyma (10% increments) ‖	1.10 (0.91 – 1.33)	1.11 (0.92 – 1.34)	1.15 (0.96 – 1.39)	1.15 (0.96 – 1.39)

*OR statistically significant at p<0.05 level.

† Cough, breathlessness, sputum production, or wheeze with frequency ≥few days/month.

‡ Participants excluded if absent HIV status at TB treatment completion (n=2), no valid baseline spirometry (n=36), no baseline CT imaging (n=20).

§ Bronchiectasis severity score (0-18): unweighted sum of 6x lobar bronchiectasis scores ranging from 0 (no bronchiectasis) to 3 (severe dilatation >3 times diameter of adjacent vessel), such that increment of 3 points represents one additional lobe with severe airway dilatation, or combination of 1-3 lobes with less severe disease.

‖Total % of parenchymal abnormalities across lung, including: parenchymal banding, atelectasis, consolidation, ground glass change, emphysema, emphysematoid destruction, cavities / cystic airspaces. Excluding mosaicism which represents airway/vascular rather than lung tissue abnormality.

Appendix 12: Factors predicting acute respiratory events over 1-year, including sensitivity analyses

Table E13: Logistic regression models of baseline parameters associated with the presence of any acute respiratory events[†] over 1-year follow up (n=335)[‡].

Variables measured at TB treatment end	Univariate OR (95% CI)	Multivariate, controlling for baseline FEV_1 [§] OR (95% CI)	Multivariate, controlling for baseline FVC [§] OR (95% CI)
Age	1.01 (0.99 – 1.04)	1.01 (0.98 – 1.04)	1.02 (0.98 -1.05)
Female sex	1.29 (0.71 – 2.36)	0.43 (0.16 – 1.18)	0.43 (0.15 – 1.19)
Height	0.96 (0.92 – 0.99)*	0.96 (0.91 – 1.01)	0.96 (0.91 – 1.02)
HIV status - Negative - Positive, CD4≥200 - Positive, CD4<200	 1.0 0.51 (0.26 – 0.996)* 0.50 (0.23 – 1.06)	 1.0 0.43 (0.20 – 0.90)* 0.34 (0.14 – 0.85)*	 1.0 0.42 (0.20 – 0.89)* 0.33 (0.13 – 0.82)*
Microbiologically proven TB	1.05 (0.52 – 2.11)	1.21 (0.56 – 2.63)	1.23 (0.56 – 2.68)
BMI (kg/m2)	0.98 (0.89 – 1.09)	1.03 (0.91 – 1.15)	1.03 (0.92 – 1.15)
Hb (g/dL)	0.90 (0.78 – 1.04)	0.86 (0.71 – 1.04)	0.86 (0.71 – 1.04)
Pack-year smoking history	0.98 (0.91 – 1.05)	0.98 (0.91 – 1.05)	0.97 (0.91 – 1.05)
Maximum education ≤ 1ry school	1.02 (0.57 – 1.84)	0.81 (0.41 – 1.61)	0.87 (0.44 – 1.70)
Respiratory symptoms ≥monthly	3.00 (1.49 – 6.04)*	2.60 (1.25 – 5.42)*	2.60 (1.25 – 5.42)*
Absolute FEV1 (100 ml increments)	0.94 (0.89 – 0.98)*	0.94 (0.88 – 1.01)	
Absolute FVC (100 ml increments)	0.95 (0.91 – 0.99)*		0.95 (0.89 – 1.02)
Bronchiectasis severity score (3-point increments, 0-6)[‖]	0.94 (0.70 – 1.27)	0.81 (0.54 – 1.22)	0.80 (0.52 – 1.21)
Abnormal parenchyma (10% increments) [††]	1.05 (0.90 – 1.23)	0.99 (0.79 – 1.25)	1.01 (0.80 – 1.27)

*OR statistically significant at p<0.05 level.

[†]Present if ≥1 acute respiratory event (an unscheduled visit to health care provider (outpatient or inpatient) due to a respiratory complaint (cough, breathlessness, sputum, wheeze, chest pain)) during 6- or 12-month study follow-up.

[‡]Participants excluded if absent HIV status at TB treatment completion (n=2), no valid baseline spirometry (n=36), no baseline HRCT imaging (n=20), or no outcome data obtained over follow-up period (n=12). Includes participants contributing either 6-month (n=13) and 12-month (n=322) follow-up.

[§]Co-linearity of FEV_1 and FVC precludes inclusion of both in a single model – separate models constructed to control for baseline level of each.

[‖]Bronchiectasis severity score (0-18): unweighted sum of 6x lobar bronchiectasis scores ranging from 0 (no bronchiectasis) to 3 (severe dilatation >3 times diameter of adjacent vessel), such that increment of 3 points represents one additional lobe with severe airway dilatation, or combination of 1-3 lobes with less severe disease.

[††]Total % of parenchymal abnormalities across lung, including: parenchymal banding, atelectasis, consolidation, ground glass change, emphysema, emphysematoid destruction, cavities / cystic airspaces. Excluding mosaicism which represents airway/vascular rather than lung tissue abnormality.

Table E14: Sensitivity analyses of logistic regression models of baseline parameters associated with the presence of any acute respiratory events† over 1-year follow up‡, with outcomes for those lost to follow-up allocated as positive or negative.

Analysis 1: Participants with 6-months follow-up only, who were not known to have already had a respiratory event, assumed to have had a respiratory event after LTFU (n=335).

Analysis 2: Participants with 6-months follow-up only who were not known to have already had a respiratory event assumed to have had a respiratory event after LTFU, AND those with no follow-up assumed to have had a respiratory event (n=347).

Analysis 3: Participants with no-follow up assumed to have had a respiratory event (n=347).

Variables measured at TB treatment end	Multivariate model, with FEV_1			Multivariate model, with FVC		
	Analyses 1	Analysis 2	Analysis 3	Analyses 1	Analysis 2	Analysis 3
Age	1.00 (0.97 – 1.04)	1.00 (0.97 – 1.03)	1.01 (0.98 – 1.05)	1.01 (0.98 – 1.04)	1.01 (0.98 – 1.04)	1.02 (0.99 – 1.05)
Female sex	0.42 (0.16 – 1.09)	0.60 (0.25 – 1.46)	0.42 (0.16 – 1.15)	0.46 (0.17 – 1.19)	0.65 (0.27 – 1.59)	0.41 (0.15 – 1.15)
Height	0.96 (0.91 – 1.01)	0.99 (0.95 – 1.04)	0.95 (0.90 -1.01)	0.96 (0.91 – 1.01)	0.99 (0.94 – 1.03)	0.96 (0.90 – 1.01)
HIV status - Negative - Positive, CD4≥200 - Positive, CD4<200	1.0 0.39 (0.19 – 0.80)* 0.40 (0.17 – 0.92)*	1.0 0.36 (0.18 – 0.72)* 0.50 (0.24 – 1.07)	1.0 0.44 (0.21 – 0.93)* 0.34 (0.14 – 0.84)*	1.0 0.39 (0.19 – 0.79)* 0.38 (0.17 – 0.88)*	1.0 0.36 (0.18 – 0.71)* 0.49 (0.23 – 1.03)*	1.0 0.44 (0.21 – 0.92)* 0.33 (0.13 – 0.81)*
Microbiologically proven TB	1.44 (0.68 – 3.02)	1.47 (0.73 – 2.94)	1.21 (0.56 – 2.62)	1.43 (0.68 – 3.01)	1.46 (0.73 – 2.93)	1.21 (0.56 – 2.64)
BMI (kg/m2)	1.06 (0.95 – 1.17)	1.03 (0.94 – 1.15)	1.03 (0.91 – 1.15)	1.05 (0.95 – 1.17)	1.04 (0.94 – 1.15)	1.03 (0.92 – 1.15)
Hb (g/dL)	0.84 (0.70 – 1.00)*	0.84 (0.71 – 1.00)*	0.87 (0.72 – 1.05)	0.84 (0.70 – 1.00)	0.84 (0.71 – 1.00)*	0.87 (0.72 – 1.05)
Pack-year smoking history	0.96 (0.89 – 1.04)*	0.95 (0.88 – 1.03)	0.98 (0.91 – 1.05)	0.96 (0.89 – 1.04)	0.95 (0.88 – 1.03)	0.98 (0.91 – 1.05)
Maximum education ≤ 1ry school	0.83 (0.44 – 1.58)	0.78 (0.43 – 1.42)	0.82 (0.41 – 1.61)	0.87 (0.46 – 1.63)	0.81 (0.45 – 1.47)	0.87 (0.44 – 1.69)
Respiratory symptoms ≥monthly	2.33 (1.21– 4.52)*	2.49 (1.34 – 4.63)*	2.45 (1.18 – 5.10)*	2.36 (1.22 – 4.56)*	2.52 (1.35 – 4.68)*	2.46 (1.18 – 5.12)*
Absolute FEV1 (100 ml increments)	0.96 (0.90 – 1.03)	0.96 (0.91 – 1.02)	0.95 (0.89 – 1.02)			
Absolute FVC (100 ml increments)				0.98 (0.93 – 1.04)	0.98 (0.93 – 1.04)	0.96 (0.90 – 1.02)
Bronchiectasis severity score (3 point increments, 0-6) §	0.75 (0.50 – 1.12)	0.77 (0.53 – 1.11)	0.82 (0.54 – 1.23)	0.75 (0.50 – 1.13)	0.77 (0.53 – 1.12)	0.80 (0.52 – 1.22)
Abnormal parenchyma (10% increments) ‖	1.00 (0.80 – 1.25)	1.01 (0.82 – 1.25)	0.99 (0.79 – 1.25)	1.03 (0.83 - 1.28)	1.04 (0.85 – 1.28)	1.01 (0.80 – 1.27)

*OR statistically significant at p<0.05 level.

†Present if ≥1 acute respiratory event (an unscheduled visit to health care provider (outpatient or inpatient) due to a respiratory complaint (cough, breathlessness, sputum, wheeze, chest pain)) documented in health passport +/- self reported during 6- or 12-month study follow-up.

‡Participants excluded if absent HIV status at TB treatment completion (n=2), no valid baseline spirometry (n=36), no baseline CT imaging (n=20), or no outcome data obtained over follow-up period (n=12). Includes participants contributing either 6-month (n=13) and 12-month (n=322) follow-up.

[§] Bronchiectasis severity score (0-18): unweighted sum of 6x lobar bronchiectasis scores ranging from 0 (no bronchiectasis) to 3 (severe dilatation >3 times diameter of adjacent vessel), such that increment of 3 points represents one additional lobe with severe airway dilatation, or combination of 1-3 lobes with less severe disease.
[‖] Total % of parenchymal abnormalities across lung, including: parenchymal banding, atelectasis, consolidation, ground glass change, emphysema, emphysematoid destruction, cavities / cystic airspaces. Excluding mosaicism which represents airway/vascular rather than lung tissue abnormality.

Appendix 13: Factors predicting spirometry at 1-year

Table E15: Linear regression model, to determine the effect of any respiratory events in the 1-year follow up period, on spirometry parameters 1-year following TB treatment completion (n=296)[†].
All univariate & multivariate models coefficients include adjustment for participant age (yrs), sex, and height (cm).

Variables	Univariate (ml, 95% CI)	Multivariate, partial model (ml, 95% CI)	Multivariate, full model (ml, 95% CI)
Absolute FEV_1 (ml) at 1-year			
HIV positive status	192.30 (69.39 – 315.21)*	173.89 (52.57 – 295.20)*	85.04 (35.68 – 134.40)
Microbiologically proven TB	-81.57 (-222.21 – 59.07)	-32.16 (-168.75 – 104.44)	-33.36 (-88.38 – 21.65)
BMI (kg/m2)	41.10 (19.72 – 62.48)*	37.83 (16.79 – 58.88)*	0.93 (-7.95 – 9.81)
Pack-year smoking history	-11.74 (-24.12 – 0.63)	-8.27 (-20.35 – 3.80)	-2.82 (-7.65 – 2.02)
Maximum education ≤ 1ry school	-138.51 (-265.89 - -11.14)*	-128.39 (-253.25 - -3.52)*	-8.25 (-58.89 – 42.38)
Respiratory symptoms ≥monthly	-181.70 (-300.56 - -62.84)*		-9.42 (-57.04 – 38.20)
Absolute FEV1 at baseline (100 ml increments)	87.80 (83.47 – 92.13)*		86.74 (81.62 – 91.86)*
Bronchiectasis severity score (3-point increments, 0-6)	-194.40 (-248.03 - -140.77)*		-5.32 (-35.04 – 24.40)
Abnormal parenchyma (10% increments)	-151.35 (-181.37 - -121.34)*		6.45 (-12.62 – 25.52)
≥1 acute respiratory event during follow-up	-202.91 (-366.66 - -39.17)*		-81.97 (-146.95 - -17.00)*
Absolute FVC (ml) at 1-year			
HIV positive status	181.00 (53.19 – 308.81)*	165.79 (38.00 – 293.58)*	108.55 (55.12 – 161.99)*
Microbiologically proven TB	-1.24 (-147.40 – 144.92)	37.50 (-106.38 – 181.38)	5.49 (-54.15 – 65.13)
BMI (kg/m2)	39.17 (16.92 – 61.42)	36.91 (14.75 – 59.08)*	-4.06 (-13.71 – 5.59)
Pack-year smoking history	-9.43 (-22.29 – 3.43)	-7.72 (-20.44 – 5.00)	-1.35 (-6.59 – 3.89)
Maximum education ≤ 1ry school	-24.09 (-157.17 – 109.00)	-19.29 (-150.82 – 112.24)	22.37 (-32.24 – 76.98)
Respiratory symptoms ≥monthly	-185.13 (-308.45 - -61.82)*		-7.55 (-59.16 – 44.05)
Absolute FVC at baseline (100 ml increments)	84.50 (80.01 – 88.99)*		85.73 (80.71 – 90.74)*
Bronchiectasis severity score (3-point increments, 0-6)	-178.93 (-235.56 - -122.31)*		-14.22 (-46.52 – 18.08)
Abnormal parenchyma (10% increments)	-127.27 (-160.15 - -94.39)*		20.95 (0.94 – 40.97)*
≥1 acute respiratory event during follow-up	-256.72 (-425.66 - -87.77)*		-121.78 (-192.19 - -51.37)*

*Co-efficients statistically significant at p<0.05 level.

[†]Participants excluded if absent HIV status at TB treatment completion (n=2), no valid baseline spirometry (n=36), no baseline HRCT imaging (n=20), no valid 12-month spirometry (n=48), or no data on events obtained over follow-up period (n=12).

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