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The effect of HIV-associated tuberculosis, tuberculosis-IRIS, and prednisone on lung function

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"Take home" message:
Post-tuberculosis lung disease is common in patients with HIV-associated TB at high risk of TB-IRIS (CD4 count < 100/µl). Neither TB-IRIS itself, nor prednisone to prevent TB-IRIS affected long term pulmonary outcomes in a South African clinical setting.

Abstract

Residual pulmonary impairment is common after treatment for tuberculosis. Lung function data in patients with HIV-associated tuberculosis are scarce, especially in the context of paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) and prophylactic prednisone. We aimed to determine the prevalence of lung function abnormalities in patients with HIV-associated tuberculosis and CD4 counts ≤ 100 cells/µl and assess the effect of prophylactic prednisone and the development of paradoxical TB-IRIS on pulmonary impairment.

We performed spirometry, six-minute walk test, and chest radiography at baseline (week 0), week 4, 12, and 28 in participants of the PredART trial, which evaluated a 28-day course of prednisone to prevent TB-IRIS in patients with HIV-associated tuberculosis commencing antiretroviral therapy.

153 participants underwent spirometry and/or six-minute walk test at one or more time points. Abnormal spirometry measurements were present in 66% of participants at week 0 and 50% at week 28; low forced vital capacity was the commonest abnormality. Chest radiographs showed little or no abnormalities in the majority of participants.
Prednisone use resulted in a 42 meters greater six-minute walk distance and a 4.9 % higher percentage of predicted forced expiratory volume in 1 second at week 4; these differences were no longer significantly different from week 12 onwards. TB-IRIS did not significantly impair lung function outcome.

Residual pulmonary impairment is common in HIV-associated tuberculosis. In patients with low CD4 counts, neither prophylactic prednisone as used in our study nor the development of TB-IRIS significantly affected week 28 pulmonary outcome.

Introduction

Tuberculosis (TB) is frequently complicated by lung function impairment. The odds of abnormal spirometric test results are 2- to 3-fold higher in patients with a history of TB compared to those without a history of TB, with both obstructive and/or restrictive impairments occuring [1, 2]. Studies of lung function in people with a history of TB found abnormal lung function in 45-87% [3-5], with even higher proportions reported in multi-drug resistant TB [6, 7]. HIV is an independent risk factor for predominantly obstructive lung function impairment [8, 9], however data on lung function impairment in HIV-associated TB are scarce, as HIV co-infected patients are frequently excluded from studies. TB-related lung damage may be less common in those co-infected with HIV, however current data are conflicting. (1) A single large study found less pulmonary impairment after TB in patients who were HIV positive patients [4], while other studies have not supported this beneficial association between HIV status and spirometric outcomes [5, 10, 11]. (2) Further, chest radiograph (CXR) findings in patients with HIV-associated TB and low CD4 counts (CD4 < 200/µl) are frequently normal or atypical [12], (3) and HIV co-infection results in lower levels of several of mediators usually implicated in inflammatory lung damage [13]. Conversely, paradoxical tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS) after the start of antiretroviral therapy (ART) causes inflammation and high levels of inflammatory mediators [14-17]. Two recent studies suggest TB-IRIS may cause lung function impairment [18, 19], one showing increased inflammation, as assessed by PET-CT scan, was associated with worse lung function outcomes [18]. However, in these cohorts only small numbers of patients developed pre-defined TB-IRIS, yet the authors hypothesize that increases in pulmonary inflammation can occur as part of not-clinically recognized TB-IRIS. To date, the only other study exploring the relationship between TB-IRIS and lung function found worse spirometric outcomes in the three patients who developed TB-IRIS compared to eleven controls [15].

Corticosteroids reduce inflammation and inhibit several of the immune mediators implicated in lung damage during TB [20-23], and may therefore reduce lung function impairment associated with TB. Previous studies assessing this association did not find a significant effect of corticosteroid use on tests of lung function [24-27]. However, most of

these studies were performed before the introduction of rifampicin, and none included HIV co-infected patients.

In this study, we determined the prevalence of lung function impairment over time in a randomized controlled trial of patients treated for HIV-associated TB. Additionally, we assessed the effect of prednisone evaluated in comparison to placebo for prevention of TB-IRIS on pulmonary outcome in this patient group.

Methods

Design and setting

This was a substudy of the PredART trial [28], a randomized, double-blind, placebo-controlled trial assessing the efficacy of prednisone to prevent TB-IRIS. Participants were recruited from Khayelitsha, a peri-urban township in Cape Town, South Africa. They were ambulant and treated in an outpatient setting. They received either prednisone or placebo (40 mg/day for 2 weeks, followed by 20 mg/day for 2 weeks), starting within 48 hours after starting ART. Study drug could be replaced with open-label prednisone (1.5 mg/kg/day for 2 weeks, followed by 0.75 mg/kg/day for 2 weeks or longer if clinically indicated) for treatment of TB-IRIS. TB-IRIS events were adjudicated by three clinical experts using the International Network for the Study of HIV-associated IRIS (INSHI) consensus case definition [29].

Enrolment for the substudy started later than the main trial. Participants already enrolled in the main trial could enrol in the substudy from their next eligible visit, if they had not completed the main trial yet. Participants treated for multi-drug resistant TB or who prematurely discontinued TB treatment were excluded from the analysis at week 28. Successful completion of TB treatment was defined following South African National Tuberculosis Management Guidelines [30].

The substudy was approved by the same ethical committees that approved the main trial [28]. Separate written informed consent was obtained.

Procedures

Substudy visits were scheduled at week 0 (initiation of ART and study drug), 4, 12, and 28. At each visit, pulmonary symptoms (cough, dyspnoea at exertion, and dyspnoea at rest) were assessed by the trial doctor and spirometry and six-minute walk test (6MWT) were performed. Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) were measured using a desktop spirometer (MIR Spirolab III, Roma, Italy). Tests were performed and results interpreted using the 2005 American Thoracic Society / European Respiratory Society guidelines for spirometry, using NHANES reference ranges [31]. We defined four possible outcomes (Figure S1): normal lung function (FEV1/FVC $\geq$ 70% and FVC $\geq$ 80% of the predicted value), low FVC (FEV1/FVC $\geq$ 70% and FVC < 80% of the predicted value), obstructive impairment with and without low FVC (FEV1/FVC < 70% of the predicted value), and 'technically incorrect', consisting of participants who performed spirometry but did not meet criteria for interpretation (Table S1). 6MWTs were performed following the 2002 American Thoracic Society guidelines [32] on a 20-meter outdoor track. CXRs were performed at week 0 and 28. After completion of the study, digitized CXRs were scored by two independent blinded readers, using an adapted version of the Timika score as described by Kriel et al [33]. Where discrepancy existed, defined as a difference in score of more than 10 points, a third reader evaluated the CXR and consensus was found using a 2-1 vote.

Statistical methods

Analyses were performed using Stata 15.1. For categorical variables the proportions and for continuous variables the medians with interquartile ranges (IQR) were estimated at different time points. Comparison of the Karnofsky Performance Score (KPS) between groups was done using a mixed effects proportional odds model. Correlation between CXR score and lung function was done using mixed effects regression (linear or logistic) models. Mixed effect models including a random intercept and covariates were used to model the evolution of pulmonary function over time. The effect of prophylactic prednisone on pulmonary function was tested using a test of the interaction of prednisone and visit number; participants receiving prednisone as treatment for TB-IRIS were analysed in their intention-to-treat arm (ie. study placebo or prednisone). The effect of TB-IRIS was tested

using a joint test of the main effect of TB-IRIS and its interaction with visit number. A p-value of < 0.05 was considered statistically significant.

Results

Between January 2015 and February 2016, 153 participants were enrolled, 77 from the prednisone arm and 76 from the placebo arm. The flow of participants is described in Figure 1; baseline characteristics are summarized in Table 1. Seventy-one participants (46%) developed TB-IRIS, 30 in the prednisone and 41 in the placebo arm; 46 (30%) participants received open-label prednisone as treatment for TB-IRIS, 16 in the prednisone and 30 in the placebo arm.

Overall prevalence of lung function abnormalities

Symptoms

Eighty percent of participants reported cough, dyspnoea on exertion, and/or dyspnoea at rest as one of their presenting TB symptoms. At week 0, a median of 16 (IQR 15-21) days into TB treatment, 50% had one or more of these symptoms. Symptoms improved over time; however, 8% of participants who successfully completed their TB treatment at week 28 still had one or more respiratory symptom (Table 2).

Spirometry

A total of 426 spirometry tests were performed. In 15 substudy participants, spirometry was not performed at one or more time points; 5 of these participants were too ill to perform spirometry, the remaining 10 were not done for logistic reasons. Spirometic outcomes at different time points are shown in Table 2. The proportion of participants with a normal spirometry outcome was 26.4% at week 0, increasing to 47.4% at week 28. Low FVC was the commonest abnormality. The proportion of participants with obstruction with or without low FVC was low and roughly the same over time. We found no effect of CD4 cell count recovery on change over time of spirometric outcomes ($p = 0.71$ for FEV1).

At week 0, 23 (21.7%) participants performed a technically incorrect test; the main reason was the inability to exhale for 6 seconds. To assess if this possibly reflected more impaired

lung function, we compared six-minute walking distance (6MWD) and KPS between participants with correctly and incorrectly performed tests. On average, the participants with an incorrect test had a 6MWD which was 56 meters (95% CI 30-83; $p < 0.001$) shorter and a lower KPS ($p < 0.001$). At week 12, 13 out of 20 participants with an initial incorrect test had obstruction and/or a low FVC; with similar findings in 11 out of 16 participants at week 28.

Six-minute walking distance

A total of 410 6MWTs were performed; 29 substudy participants did not perform a walking test at one or more time points, main reasons being painful feet or rain. Median 6MWD was 520 meters (IQR 465-576) at week 0 and 585 meters (IQR 520-655) at week 28 (Table 2).

Chest radiograph score

CXR scores were available for 135 participants at week 0, and for 61 participants at week 28. Possible scores ranged from 0 to 140, with higher scores indicating more CXR abnormalities. The median CXR scores were low: 4.0 (IQR 0.8-11.7) at week 0, and 0.9 (IQR 0-3.75) at week 28 (Table 2). Cavities were present in 8 (6%) participants at week 0 and 1 (2%) participant at week 28. Overall, CXR scores showed significant correlation with respiratory symptoms, 6MWD and FEV1: for an increase of 10 points in CXR score, an OR of 1.51 for symptoms (95% CI 1.13-2.03; $p = 0.006$) was observed (Table S2); the average 6MWD decreased by 21 meters (95% CI 11-31; $p < 0.001$); and the average FEV1 percentage of predicted decreased by 3.3 % (95% CI 1.9-4.8; $p<0.001$). However, in CXRs with lower scores (i.e. below 10), the FEV1 varied markedly, and both normal and impaired lung function were seen in participants with little or no CXR abnormalities (Figure S2).

There was no significant association between CXR score at week 0 and spirometry results at week 28 (OR for normal lung function at week 28 per 10 points increase in CXR score at week 0 was 0.77 (95% CI 0.55-1.08; $p = 0.13$); and average FEV1 percentage of predicted at week 28 was 1.87% lower (95% CI 3.98 - -0.24; $p = 0.08$) for every 10-point increase of week 0 CXR score).

Effect of prednisone

There was no statistically significant difference in the change over time of symptoms (p=0.13) or CXR score (p=0.92) between the prednisone and the placebo arm. The change in 6MWD over time was statistically significantly different between the groups (p=0.03), with the largest difference at week 4: participants in the prednisone arm walked 42 (95% CI 13-72) meters further compared to participants in the placebo arm. Change over time of both FEV1 and FVC were also statistically significantly different between the two arms (p = 0.03 and p = 0.01), once again most obvious at week 4, with those in the prednisone arm having a FEV1 percentage of predicted that was 4.9% (95% CI 0.7-9.0%) higher and a FVC percentage of predicted that was 4.9% (95% CI1.3-8.5%) higher at week 4 compared to those in the placebo arm. Adjusting for the use of prednisone as treatment for TB-IRIS gave similar results (Table S3). Baseline lung function did not statistically significantly affect the impact of prednisone (p = 0. 56 for FEV1) (Table S4). At week 28, there was no longer a clear difference in either the 6MWD or FEV1 and FVC between the arms (Figure 2 and Tables 3 and S5).

Effect of TB-IRIS

When comparing participants who developed paradoxical TB-IRIS to those who did not, TB-IRIS was associated with a change in the presence of symptoms over time (p = 0.03), but there was no statistically significant difference in change over time of FEV1 percentage of predicted (p = 0.11), FVC percentage of predicted (p = 0.054), 6MWD (p = 0.62), or CXR score (p = 0.20) (Figure 3 and Tables 4 and S6).

Sixteen participants developed TB-IRIS without any respiratory signs or symptoms. Exclusion of these non-pulmonary IRIS cases from the analysis did not affect the results (data not shown).

Discussion

We assessed pulmonary function in a cohort of patients with HIV-associated TB at high risk for TB-IRIS, enrolled in a trial investigating the efficacy of prophylactic prednisone in preventing TB-IRIS.

Respiratory symptoms were common early during TB treatment and abnormal spirometry (low FVC and airflow obstruction with and without low FVC) was found in 66% of participants with acceptable spirometry. At the end of TB treatment, symptoms persisted in 8% and abnormal spirometry in 50% of participants. The proportion of abnormal spirometry results is higher than expected for either the general or HIV-infected population [1, 34], but is comparable to results from other studies in HIV-associated TB patients [4, 5, 19].

In our trial, open-label treatment of TB-IRIS with prednisone was allowed. This resulted in 30/76 participants in the placebo arm receiving prednisone for the treatment of TB-IRIS and the majority of the participants who developed TB-IRIS receiving prednisone, either as prophylaxis, as treatment, or both, with prednisone treatment given to the more severe cases of TB-IRIS. This limits our evaluation of the individual effects of both prednisone as well as TB-IRIS on lung function.

Within these limitations, we did not find an effect of TB-IRIS on spirometric lung function over time. This contradicts findings of two recent studies [18, 19] that hypothesized that TB-IRIS-like increases in inflammation may lead to decreased lung function, which may occur in patients with HIV-associated TB initiating ART, even in the absence of clinically overt TB-IRIS. It is possible that in the present study, mild TB-IRIS did not result in sufficient additional pulmonary inflammation to affect long-term respiratory outcomes, whereas in severe TB-IRIS the effect was ameliorated by treatment with prednisone.

We found prophylactic prednisone affected change over time of both 6MWD and FEV1 and FVC, primarily at week 4, when participants completed their study prednisone, potentially by preventing TB-IRIS. Consequently, the higher proportion of participants with TB-IRIS in the placebo arm may be responsible for the demonstrated favourable effect of prophylactic prednisone on lung function. Additionally, prednisone can directly improve exercise performance [36] and FEV1 in other disease processes, for example acute exacerbations of chronic obstructive pulmonary disease (COPD) [37]. Ravimohan et al [18] found that decreased lung function after 4 weeks of TB treatment, impacts negatively on long-term lung function, and Auld et al [19] found similar associations, but only in severe lung function

declines. In the current study, despite an increase in lung function at week 4, we did not observe any long-term effects of prophylactic prednisone on lung function. This could be due to type 2 error, with large proportion of participants in the placebo arm receiving prednisone as treatment for TB-IRIS. Alternatively, prednisone may have been given too late in the disease process and prescribed only after lung damage had already occurred.

We found a high proportion of participants with technically incorrect spirometry results early on during treatment – a finding not reported previously. In studies performed in participants without TB, in the latter stages of TB treatment or after TB treatment, 2-30% did not perform spirometry correctly and these patients were subsequently excluded [1, 3-5, 9, 18, 38]. We considered that the participants who did not perform spirometry correctly might include those with worse pulmonary status: for example, in severely ill patients, and in those with significant cough and/or shortness of breath spirometry is technically challenging. This hypothesis was supported in our study by finding that the majority of technically incorrect spirometric results were due to inability of patients to exhale for six seconds. Further, the association with a shorter 6MWD and a lower KPS, and abnormal lung function in the majority of these participants at follow-up spirometry testing adds weight to this argument. Thus, excluding these participants from the analyses may underestimate the burden of lung function impairment in TB. In our study, when technically incorrect were included as abnormal, the percentage abnormal tests at baseline increased from 66% to 74%.

In keeping with published data on HIV-associated TB patients with a low-CD4 count [12], only a small proportion of participants demonstrated extensive CXR abnormalities, while cavitation was uncommon. Our finding of a negative association between CXR score and FEV1, although statistically significant, needs to be interpreted with caution. Although a high score is unsurprisingly associated with lower FEV1, a low score does not appear to rule out significant abnormality in FEV1. Several other studies, using many different scoring methods, have reported the relationship between FEV1 and CXR score in TB [3, 5, 10, 39, 40]. However, all studies describe more severe CXR abnormalities than our present study, and few included HIV positive patients. Those that did, chose not to report data on HIV patients specifically, or claimed the numbers were too small for meaningful sub-analysis.

Our observation that the presence of a normal CXR in HIV-associated TB patients with a CD4 count < 100 cells/µl does not exclude lung function abnormalities, is likely explained by the insensitivity of CXR to detect changes responsible for the reduced FEV1, for example small airways and subtle parenchymal abnormalities.

Besides the considerable overlap between participants developing TB-IRIS and participants prescribed prednisone to treat TB-IRIS, our study has other limitations. First, as consequence of the substudy commencing after the main trial, we do not have complete data on all participants. Second, we do not have reliable information about the time between the start of symptoms and the start of TB treatment, with longer duration of symptoms being a risk factor for pulmonary impairment [5, 41]. Third, normal values for 6MWD in our population are lacking. Most participants walked relatively far, possibly because of the relatively short duration of illness and possibly younger age of participants when compared with other chronic lung diseases. Finally, the use of the NHANES reference range (derived in North American populations) may have resulted in an overestimate of lung function impairment, as normal values for FEV1 and FVC tend to be higher than those for African populations [35].

In conclusion, we found that lung function impairment is common in patients with HIV-associated TB. Prednisone to prevent TB-IRIS improved lung function at week 4, possibly by reducing TB-IRIS, however, the 28-day course of prednisone did not improve lung function from week 12 onwards in patients with CD4 counts < 100 cells /µl. Overlap between the groups through the development of TB-IRIS and subsequent use of prednisone as treatment, limits our ability to make definitive conclusions. Prednisone remains recommended to prevent TB-IRIS in this population based on the findings of the main PredART trial [28], despite this study being unable to demonstrate long term benefits in lung function. Further studies, using PET-CT imaging and other biomarkers of inflammation and lung damage in TB [13] are needed to better understand the pathogenesis of lung function impairment in HIV-associated TB.

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References

1. Pefura-Yone EW, Balkissou AD, Kengne AP. Determinants of Restrictive Spirometric Pattern in a Sub-Saharan Urban Setting: A Cross-sectional Population-based Study. *Open Respir Med J* 2016: 10: 86-95.
2. Allwood BW, Myer L, Bateman ED. A systematic review of the association between pulmonary tuberculosis and the development of chronic airflow obstruction in adults. *Respiration* 2013: 86(1): 76-85.
3. Akkara SA, Shah AD, Adalja M, Akkara AG, Rathi A, Shah DN. Pulmonary tuberculosis: the day after. *Int J Tuberc Lung Dis* 2013: 17(6): 810-813.
4. Manji M, Shayo G, Mamuya S, Mpembeni R, Jusabani A, Mugusi F. Lung functions among patients with pulmonary tuberculosis in Dar es Salaam - a cross-sectional study. *BMC Pulm Med* 2016: 16(1): 58.
5. Mbatchou Ngahane BH, Nouyep J, Nganda Motto M, Mapoure Njankouo Y, Wandji A, Endale M, Afane Ze E. Post-tuberculous lung function impairment in a tuberculosis reference clinic in Cameroon. *Respir Med* 2016: 114: 67-71.
6. de Valliere S, Barker RD. Residual lung damage after completion of treatment for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2004: 8(6): 767-771.
7. Singla R, Mallick M, Mrigpuri P, Singla N, Gupta A. Sequelae of pulmonary multidrug-resistant tuberculosis at the completion of treatment. *Lung India* 2018: 35(1): 4-8.
8. Fitzpatrick ME, Kunisaki KM, Morris A. Pulmonary disease in HIV-infected adults in the era of antiretroviral therapy. *AIDS* 2018: 32(3): 277-292.
9. Pefura-Yone EW, Fodjeu G, Kengne AP, Roche N, Kuaban C. Prevalence and determinants of chronic obstructive pulmonary disease in HIV infected patients in an African country with low level of tobacco smoking. *Respir Med* 2015: 109(2): 247-254.
10. Ralph AP, Kenangalem E, Waramori G, Pontororing GJ, Sandjaja, Tjitra E, Maguire GP, Kelly PM, Anstey NM. High morbidity during treatment and residual pulmonary disability in pulmonary tuberculosis: under-recognised phenomena. *PLoS One* 2013: 8(11): e80302.
11. Fiogbe AA, Agodokpessi G, Tessier JF, Affolabi D, Zannou DM, Ade G, Anagonou S, Raherison-Semjen C, Marcy O. Prevalence of lung function impairment in cured pulmonary tuberculosis patients in Cotonou, Benin. *Int J Tuberc Lung Dis* 2019: 23(2): 195-202.
12. Kwan CK, Ernst JD. HIV and tuberculosis: a deadly human syndemic. *Clin Microbiol Rev* 2011: 24(2): 351-376.
13. Stek C, Allwood B, Walker NF, Wilkinson RJ, Lynen L, Meintjes G. The Immune Mechanisms of Lung Parenchymal Damage in Tuberculosis and the Role of Host-Directed Therapy. *Front Microbiol* 2018: 9: 2603.
14. Nakiwala JK, Walker NF, Diedrich CR, Worodria W, Meintjes G, Wilkinson RJ, Mayanja-Kizza H, Colebunders R, Kestens L, Wilkinson KA, Lowe DM. Neutrophil Activation and Enhanced Release of Granule Products in HIV-TB Immune Reconstitution Inflammatory Syndrome. *J Acquir Immune Defic Syndr* 2018: 77(2): 221-229.
15. Ravimohan S, Tamuhla N, Kung SJ, Nfanyana K, Steenhoff AP, Gross R, Weissman D, Bisson GP. Matrix Metalloproteinases in Tuberculosis-Immune Reconstitution Inflammatory Syndrome and Impaired Lung Function Among Advanced HIV/TB Co-infected Patients Initiating Antiretroviral Therapy. *EBioMedicine* 2016: 3: 100-107.
16. Walker NF, Wilkinson KA, Meintjes G, Tezera LB, Goliath R, Peyper JM, Tadokera R, Opondo C, Coussens AK, Wilkinson RJ, Friedland JS, Elkington PT. Matrix Degradation in Human Immunodeficiency Virus Type 1-Associated Tuberculosis and Tuberculosis Immune

Reconstitution Inflammatory Syndrome: A Prospective Observational Study. *Clin Infect Dis* 2017: 65(1): 121-132.
17. Lai RP, Meintjes G, Wilkinson RJ. HIV-1 tuberculosis-associated immune reconstitution inflammatory syndrome. *Semin Immunopathol* 2016: 38(2): 185-198.
18. Ravimohan S, Auld SC, Maenetje P, Ratsela N, Mlotshwa M, Ncube I, Smith JP, Vangu MD, Sebe M, Kossenkov A, Weissman D, Wallis RS, Churchyard G, Kornfeld H, Bisson GP. Lung injury on antiretroviral therapy in adults with HIV/TB. *Clin Infect Dis* 2019.
19. Auld SC, Maenetje P, Ravimohan S, Weissman D, Ncube I, Mlotshwa M, Ratsela N, Chase W, Vangu MD, Wallis R, Churchyard G, Kornfeld H, Bisson GP. Declines in Lung Function After Antiretroviral Therapy Initiation in Adults With Human Immunodeficiency Virus and Tuberculosis: A Potential Manifestation of Respiratory Immune Reconstitution Inflammatory Syndrome. *Clin Infect Dis* 2019.
20. Bongiovanni B, Mata-Espinosa D, D'Attilio L, Leon-Contreras JC, Marquez-Velasco R, Bottasso O, Hernandez-Pando R, Bay ML. Effect of cortisol and/or DHEA on THP1-derived macrophages infected with Mycobacterium tuberculosis. *Tuberculosis (Edinb)* 2015: 95(5): 562-569.
21. Mayanja-Kizza H, Jones-Lopez E, Okwera A, Wallis RS, Ellner JJ, Mugerwa RD, Whalen CC, Uganda-Case Western Research C. Immunoadjuvant prednisolone therapy for HIV-associated tuberculosis: a phase 2 clinical trial in Uganda. *J Infect Dis* 2005: 191(6): 856-865.
22. Meintjes G, Skolimowska KH, Wilkinson KA, Matthews K, Tadokera R, Conesa-Botella A, Seldon R, Rangaka MX, Rebe K, Pepper DJ, Morroni C, Colebunders R, Maartens G, Wilkinson RJ. Corticosteroid-modulated immune activation in the tuberculosis immune reconstitution inflammatory syndrome. *Am J Respir Crit Care Med* 2012: 186(4): 369-377.
23. Tadokera R, Meintjes GA, Wilkinson KA, Skolimowska KH, Walker N, Friedland JS, Maartens G, Elkington PT, Wilkinson RJ. Matrix metalloproteinases and tissue damage in HIV-tuberculosis immune reconstitution inflammatory syndrome. *Eur J Immunol* 2014: 44(1): 127-136.
24. Malik SK, Martin CJ. Tuberculosis, corticosteroid therapy, and pulmonary function. *Am Rev Respir Dis* 1969: 100(1): 13-18.
25. Marcus H, Yoo OH, Akyol T, Williams MH, Jr. A randomized study of the effects of corticosteroid therapy on healing of pulmonary tuberculosis as judged by clinical, roentgenographic, and physiologic measurements. *Am Rev Respir Dis* 1963: 88: 55-64.
26. Angel JH, Chu LS, Lyons HA. Corticotropin in the treatment of tuberculosis. A controlled study. *Arch Intern Med* 1961: 108: 353-369.
27. Park IW, Choi BW, Hue SH. Prospective study of corticosteroid as an adjunct in the treatment of endobronchial tuberculosis in adults. *Respirology* 1997: 2(4): 275-281.
28. Meintjes G, Stek C, Blumenthal L, Thienemann F, Schutz C, Buyze J, Ravinetto R, van Loen H, Nair A, Jackson A, Colebunders R, Maartens G, Wilkinson RJ, Lynen L, Pred ARTTT. Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS. *N Engl J Med* 2018: 379(20): 1915-1925.
29. Meintjes G, Lawn SD, Scano F, Maartens G, French MA, Worodria W, Elliott JH, Murdoch D, Wilkinson RJ, Seyler C, John L, van der Loeff MS, Reiss P, Lynen L, Janoff EN, Gilks C, Colebunders R, International Network for the Study of HIVaI. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis* 2008: 8(8): 516-523.
30. National Tuberculosis Management Guidelines *In:* Department of Health RoSA, ed., 2014.

31. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, Force AET. Standardisation of spirometry. *Eur Respir J* 2005: 26(2): 319-338.
32. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002: 166(1): 111-117.
33. Kriel M, Lotz JW, Kidd M, Walzl G. Evaluation of a radiological severity score to predict treatment outcome in adults with pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2015: 19(11): 1354-1360.
34. Gupte AN, Wong ML, Msandiwa R, Barnes GL, Golub J, Chaisson RE, Hoffmann CJ, Martinson NA. Factors associated with pulmonary impairment in HIV-infected South African adults. *PLoS One* 2017: 12(9): e0184530.
35. Musafiri S, van Meerbeeck JP, Musango L, Derom E, Brusselle G, Joos G, Rutayisire C. Spirometric reference values for an East-African population. *Respiration* 2013: 85(4): 297-304.
36. Arlettaz A, Portier H, Lecoq AM, Rieth N, De Ceaurriz J, Collomp K. Effects of short-term prednisolone intake during submaximal exercise. *Med Sci Sports Exerc* 2007: 39(9): 1672-1678.
37. Singh JM, Palda VA, Stanbrook MB, Chapman KR. Corticosteroid therapy for patients with acute exacerbations of chronic obstructive pulmonary disease: a systematic review. *Arch Intern Med* 2002: 162(22): 2527-2536.
38. North CM, Muyanja D, Kakuhikire B, Tsai AC, Tracy RP, Hunt PW, Kwon DS, Christiani DC, Okello S, Siedner MJ. Systemic Inflammation, Immune Activation and Impaired Lung Function among People Living with HIV in Rural Uganda. *J Acquir Immune Defic Syndr* 2018.
39. Baez-Saldana R, Lopez-Arteaga Y, Bizarron-Muro A, Ferreira-Guerrero E, Ferreyra-Reyes L, Delgado-Sanchez G, Cruz-Hervert LP, Mongua-Rodriguez N, Garcia-Garcia L. A novel scoring system to measure radiographic abnormalities and related spirometric values in cured pulmonary tuberculosis. *PLoS One* 2013: 8(11): e78926.
40. Plit ML, Anderson R, Van Rensburg CE, Page-Shipp L, Blott JA, Fresen JL, Feldman C. Influence of antimicrobial chemotherapy on spirometric parameters and pro-inflammatory indices in severe pulmonary tuberculosis. *Eur Respir J* 1998: 12(2): 351-356.
41. Gandhi K, Gupta S, Singla R. Risk factors associated with development of pulmonary impairment after tuberculosis. *Indian J Tuberc* 2016: 63(1): 34-38.

Tables

TABLE 1 Baseline characteristics and participants developing TB-IRIS and receiving prednisone as treatment according to trial arm

	Prednisone	**Placebo**
Male	49 (64%)	41 (54%)
Age (years)	38 (31-43)	38 (31-44)
CD4 count (cells/µl)	46 (24-81)	50 (24-86)
HIV viral load (log_{10} copies/ml)	5.5 (5.2-5.8)	5.6 (5.3-5.9)
Extra-pulmonary TB (N=123)	24 (38%)	33 (55%)
Microbiologically confirmed TB	53 (70%)	59 (79%)
Previous TB	6 (8%)	8 (11%)
Time on TB treatment at week 0 (days)	16 (15-22)	16 (14-21)
Smoking status at week 0 / py *(N=127)*		
Never smoked	36 (55%)	41 (67%)
Ever smoked	30 (45%) / 2.2 (0.8-5.0)	20 (33%) / 3.75 (1.0-10.0)
Previous lung disease	1 (1.3%)	0 (0%)
Spirometry		
FEV1 (% of predicted)	75 (61-88)	73 (59-86)
FVC (% of predicted)	74 (66-89)	73 (65-81)
FVC/FEV1 (%)	83 (79-85)	82 (77-86)
TB-IRIS	30 (39%)	41 (54%)
Treatment with open-label prednisone for suspected TB-IRIS	16 (21%)	30 (39%)

TB = tuberculosis, pulmonary tuberculosis = participants with one or more pulmonary signs or symptoms (such as cough, shortness of breath, abnormal chest radiographs) of tuberculosis at presentation, extrapulmonary tuberculosis = participants with signs of extrapulmonary tuberculosis (such as pleural effusion or enlarged lymph nodes), microbiologically confirmed TB = participants with *Mycobacterium tuberculosis* detected on culture, with the use of the Xpert MTB/RIF assay (Cepheid), or as positive acid-fast bacilli on smear microscopy, py = packyear. Data are shown as number (percentage) or median (interquartile range).

TABLE 2 Symptoms, spirometric outcomes, 6MWD and CXR score in the whole study group at different time points

	week 0		week 4		week 12		week 28	
Symptoms (*N*)	*107*		*99*		*110*		*111*	
cough	40	(37.4%)	29	(29.3%)	14	(12.7%)	5	(4.5%)
dyspnoea at exertion	37	(34.6%)	27	(27.3%)	12	(10.9%)	5	(4.5%)
dyspnoea at rest	11	(10.3%)	8	(8.1%)	3	(2.7%)	1	(0.9%)
total	54	(50.5%)	43	(43.4 %)	20	(18.2%)	9	(8.1%)
Spirometry outcome (*N*)	*106*		*96*		*110*		*114*	
normal	28	(26.4%)	36	(37.5%)	50	(45.5%)	54	(47.4%)
low FVC	48	(45.3%)	42	(43.8%)	43	(39.1%)	44	(38.6%)
obstruction +/- low FVC	7	(6.6%)	7	(7.3%)	10	(9.1%)	11	(9.7%)
technically incorrect	23	(21.7%)	11	(11.5%)	7	(6.4%)	5	(4.4%)
6MWD (*N*)	*102*		*91*		*104*		*113*	
	520	(465-576)	524	(450-579)	539	(483-608)	585	(520-655)
CXR score (*N*)	*135*						*61*	
	4	(0.8-11.7)					0.9	(0-3.75)

N = total number of participants per test per visit; Symptoms total = cough, and/or dyspnea at exertion, and/or dyspnea at rest; normal = FEV1/FVC ≥ 70% *and* FVC ≥ 80% of the predicted value; low FVC = FEV1/FVC ≥ 70% *and* FVC < 80% of the predicted value; obstruction +/- low FVC = FEV1/FVC < 70%; technically incorrect = test not fulfilling criteria for interpretation; 6MWD = six-minute walk distance in meters; CXR = chest X-ray; week 0 = the start day of anti-retroviral therapy and prednisone/placebo (median 16 days after start of antituberculosis treatment). Data are shown as number (percentage) or median (interquartile range).

TABLE 3 The effect of prednisone prophylaxis on change over time of pulmonary function parameters

Change over time of six-minute walking distance (6MWD) in meters

	6MWD	95% CI	
Intercept (average 6MWD at week 0 for non-smokers)	504	484 – 523	
	Mean change in 6MWD	**95% CI**	**p-value**
Effect of smoking (ever vs never)	14	-11 – 39	0.275
	Mean change in 6MWD from week 0	**95% CI**	**p-value**
Effect of time (visit)			<0.0001
week 4	-27	-50 – -3	
week 12	32	10 – 54	
week 28	64	42 – 86	
Effect of prophylactic prednisone			0.034
week 4	42	13 – 72	
week 12	2	-26 – 30	
week 28	13	-15 – 41	

Change over time of forced expiratory volume in 1 second (FEV1) as % of predicted value

	FEV1 %	95% CI	
Intercept (average FEV1 % at week 0 for non-smokers)	76.9	73.6 – 80.2	
	Mean change in FEV1 %	**95% CI**	**p-value**
Effect of smoking (ever vs never)	-4.7	-8.8 – -0.5	0.027
	Mean change in FEV1 % from week 0	**95% CI**	**p-value**
Effect of time (visit)			<0.0001
week 4	-1.1	-4.4 – 2.1	
week 12	3.3	0.2 – 6.4	
week 28	6.8	3.6 – 10.0	
Effect of prophylactic prednisone			0.029
week 4	4.9	0.7 – 9.0	
week 12	-0.4	-4.4 – 3.5	
week 28	-1.5	-5.6 – 2.6	

Intercept and estimated coefficients with their 95% confidence intervals (95% CI) from the mixed effects regression models are listed. Data are adjusted for all other covariates presented in the table. Effect of time (visit) refers to the effect of time in the placebo arm. Because allocation to either the prednisone or the placebo arm was randomized, no adjustment for baseline variables other than smoking was done.

TABLE 4 The effect of tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) on change over time of pulmonary function parameters

Change over time of six-minute walking distance (6MWD) in meters

	6MWD	95% CI	p-value
Intercept (average 6MWD if all other co-variates are 0)	837	711-964	

	Mean change in 6MWD	95% CI	p-value
Effect of TB-IRIS at week 0	-4	-35 - 27	0.79
Effect of smoking (ever vs never)	-44	-69 – -19	0.001
Effect of age (per increase of one year in age at week 0)	-3	-4 – -2	<0.001
Effect of gender (female vs male)	-112	-138 – -86	<0.001
Effect of type of TB (participants without signs of extrapulmonary TB vs those with signs of extrapulmonary TB)	30	-14 – 74	0.19
Effect of HIV viral load (per $\log_{10}$ cps/ml increase at screening)	-32	-50 - -13	0.001
Effect of CD4 count (per increase of 10 CD4 cells/µl at screening)	-2	-4 – 1	0.21
Effect of previous tuberculosis	-21	-60 – 18	0.28

	Mean change in 6MWD from week 0	95% CI	p-value
Effect of time (visit)			<0.0001
week 4	-16	-45 – 14	
week 12	40	13 – 67	
week 28	72	44 – 100	
Effect of TB-IRIS			0.68
week 4	-21	-54 – 13	
week 12	-11	-44 – 21	
week 28	-7	-40 – 27	
Effect of prophylactic prednisone			0.036
week 4	41	13 – 70	
week 12	0	-27 – 26	
week 28	4	-22 – 31	

Change over time of forced expiratory volume in 1 second (FEV1) as % of predicted value

	FEV1 %	95% CI	p-value
Intercept (average FEV1 % if all other co-variates are 0)	83.9	57.5-110.3	

	Mean change in FEV1 %	95% CI	p-value
Effect of TB-IRIS at week 0	3.2	-2.7 – 9.2	0.29
Effect of smoking (ever vs never)	-5.9	-10.6 – -1.1	0.02
Effect of age (per increase of one year in age at week 0)	0.04	-0.2 – 0.3	0.76
Effect of gender (female vs male)	-3.6	-9.0 – 1.8	0.19
Effect of type of TB (participants without signs of extrapulmonary TB vs those with signs of extrapulmonary TB)	0.7	-8.6 – 10.1	0.88

Effect of HIV viral load (per log_{10} cps/ml increase at screening)	-0.5	-4.5 – 3.4	0.79
Effect of CD4 count (per increase of 10 CD4 cells/µl at screening)	-0.8	-1.3 – -0.2	0.005
Effect of previous tuberculosis	-14.8	-23.4 – -6.1	0.001

	Mean change in FEV1 % from week 0	**95% CI**	**p-value**
Effect of time (visit)			<0.001
week 4	1.4	-3.0 – 5.7	
week 12	6.3	2.3 – 10.4	
week 28	8.1	3.9 – 12.3	
Effect of TB-IRIS			0.06
week 4	-4.7	-9.4 – -0.1	
week 12	-6.0	-10.5 – -1.4	
week 28	-2.8	-7.6 – 2.0	
Effect of prophylactic prednisone			0.07
week 4	4.4	0.2 – 8.7	
week 12	-0.1	-4.8– 3.2	
week 28	-1.3	-5.5 – 2.8	

Intercept and estimated coefficients with their 95% confidence intervals (95% CI) from the mixed effects regression models are listed. Data are adjusted for all other covariates presented in the table.

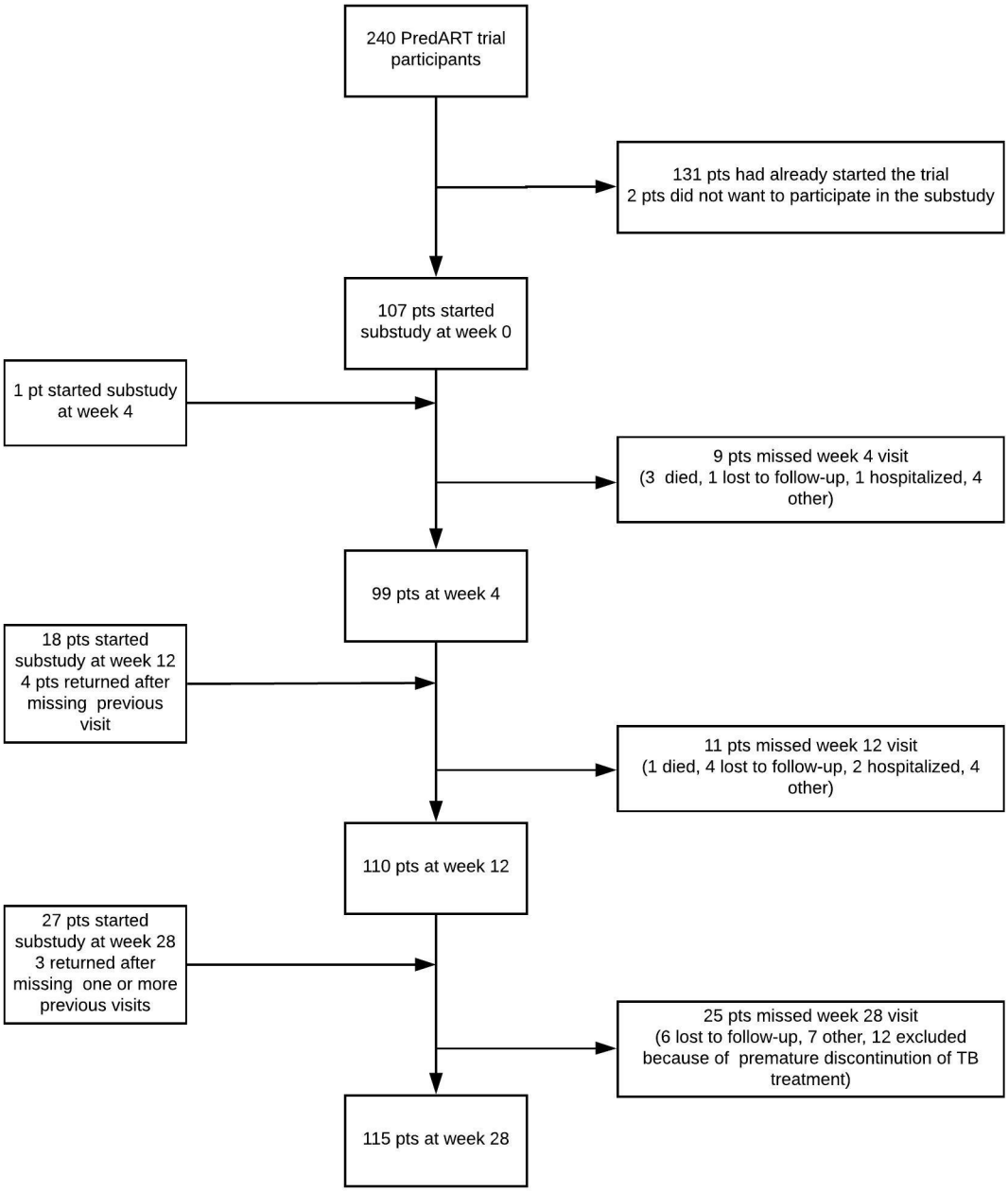
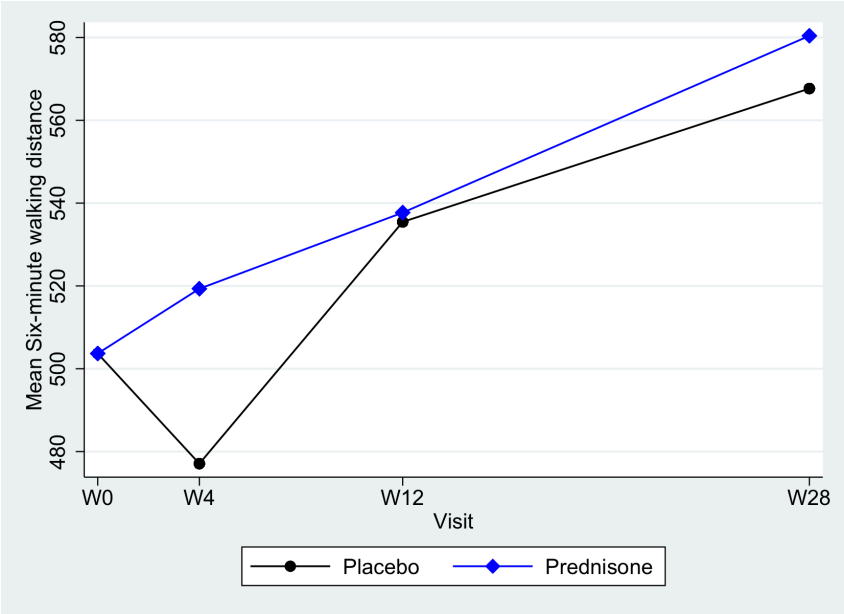


Figure 1 Number of participants per visit

A



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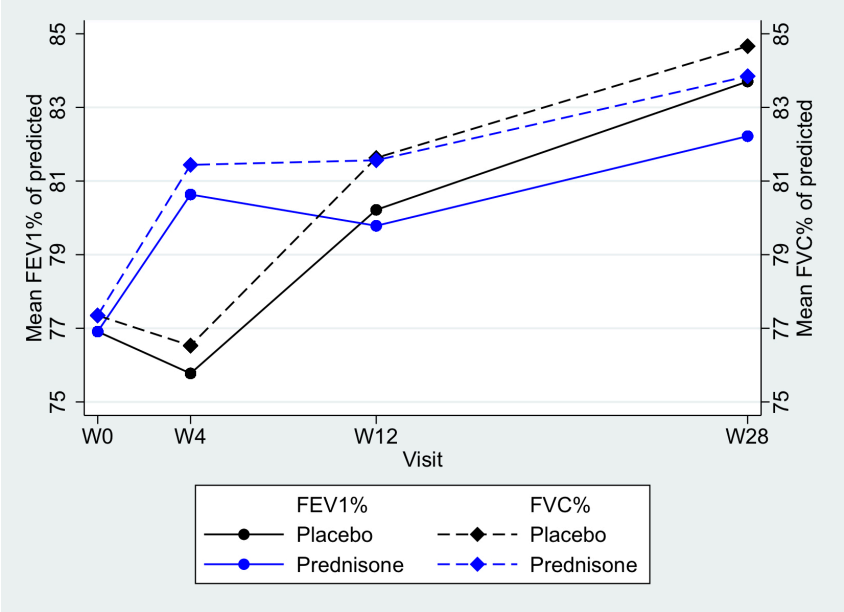
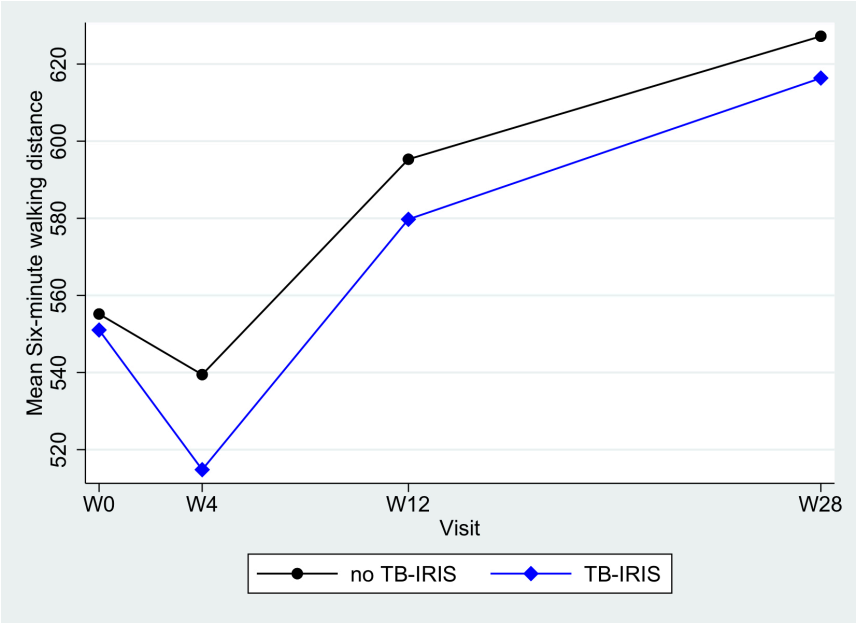


Figure 2 The effect of prednisone prophylaxis to prevent TB-IRIS on lung function. Patients treated for HIV-associated TB received either prednisone (in blue) or identical placebo (in black) during the first 4 weeks of antiretroviral therapy. Week 0 is the day when antiretroviral therapy and prednisone or placebo were started. (A) Change over time of six-minute walk distance was statistically significantly associated with prednisone use (p = 0.034). (B) Change over time of FEV1 and FVC percentage of predicted was statistically significantly associated with prednisone use (p=0.029 & p=0.015, respectively). Graphs represent data for non-smokers. Curves for smokers are parallel.

A



B

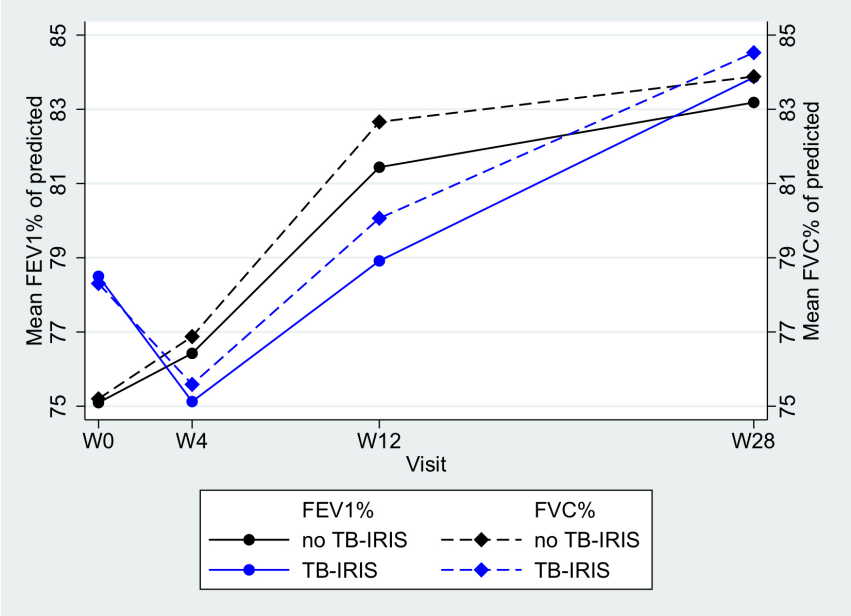


Figure 3 The effect of the development of tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) on lung function. Patients with TB-IRIS (blue) are compared to those without TB-IRIS (black). (A) Change over time of six-minute walk distance was not statistically significantly associated with TB-IRIS (p = 0.62). (B) Change over time of FEV1 and FVC percentage of predicted was not statistically significantly associated with TB-IRIS (p = 0.11 & p = 0.054, respectively)). Graphs represent data for male non-smokers in the placebo arm of age 40 who have pulmonary TB, an HIV viral load at screening of 800000 copies/ml, a CD4 at screening of 100 cells/µl and did not have previous TB. The difference between TB-IRIS and no TB-IRIS were similar for other patient profiles.

The effect of HIV-associated tuberculosis, tuberculosis-IRIS and prednisone on lung function

Cari Stek, Brian Allwood, Elsa du Bruyn, Jozefien Buyze, Charlotte Schutz, Friedrich Thienemann, Adele Lombard, Robert J. Wilkinson, Graeme Meintjes and Lutgarde Lynen

Online supplement

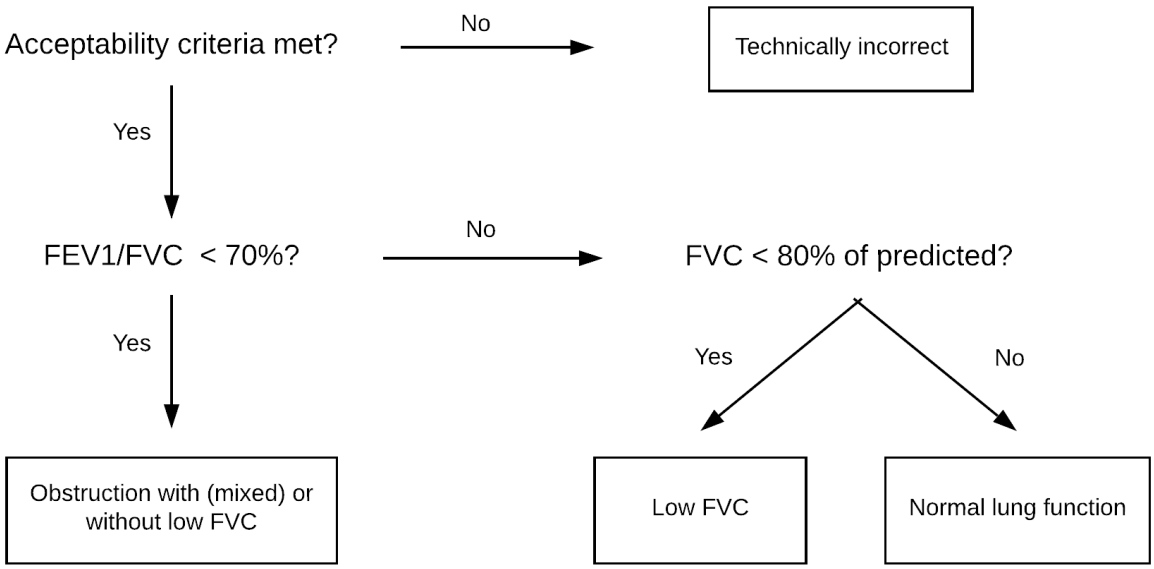


Figure S1 Definitions of different spirometry outcomes

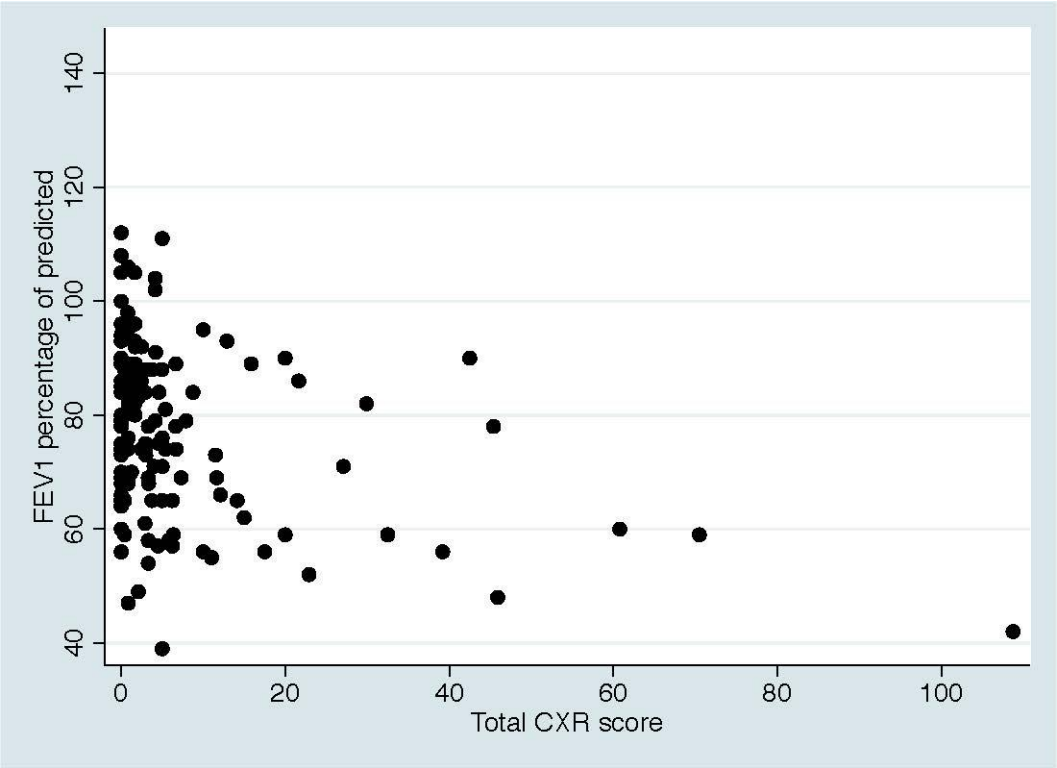


Figure S2 The association between chest X-ray score and FEV1 percentage of predicted
(n = 135). Chest X-rays were scored using an adapted version of the Timika score[1)]: visible lung fields on the chest X-ray were divided into six zones and the percentage of affected lung in each zone and its prominent opacification type were estimated. A total score was generated by adding up the percentages of each zone and dividing the total by the number of scored zones (usually 6), adding an additional 40 points if one or more cavities > 1cm in diameter were present. Therefore, total scores could range from 0 to 140. Chest X-ray scores were statistically significantly correlated with FEV1 percentage of predicted ($p < 0.001$).

[1)] Kriel M, Lotz JW, Kidd M, Walzl G. Evaluation of a radiological severity score to predict treatment outcome in adults with pulmonary tuberculosis. Int J Tuberc Lung Dis 2015: 19(11): 1354-1360

TABLE S1 Acceptability criteria for the recording of FVC and FEV1 using spirometry

No artefacts	Coughing during first second of expiration Glottis closure Early termination or submaximal effort Leak Obstructed mouthpiece
Good starts	Extrapolated volume < 5% of FVC or 0,15l, whichever is greater
Exhalation	Duration ≥ 6 s, plateau in the volume-time curve, or if the subject cannot or should not continue

Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, Force AET. Standardisation of spirometry. *Eur Respir J* 2005; 26: 319-338

TABLE S2 Association between chest X-ray score and respiratory symptoms

	Odds ratio	p-value
Cough	1.24	0.08
Dyspnoea at exertion	1.45	0.007
Dyspnoea at rest	1.03	0.89
Total	1.51	0.006

Total = cough, and/or dyspnea at exertion, and/or dyspnea at rest. Odds ratio's are calculated for an increase of 10 units in chest-X-ray score. A p-value of < 0.05 is considered significant.

TABLE S3 The effect of prednisone prophylaxis on change over time of pulmonary function parameters, adjusted for prednisone as treatment

Change over time of six-minute walking distance (6MWD) in meters

	6MWD	95% CI	p-value
Intercept (average 6MWD if all other co-variates are 0)	662	595 – 729	
	Mean change in 6MWD	**95% CI**	**p-value**
Effect of prednisone as treatment	-20	-44 - 4	0.097
Effect of smoking (ever vs never)	-45	-70 - -20	<0.001
Effect of age (per increase of one year in age at week 0)	-3	-4 – -1	<0.001
Effect of gender (female vs male)	-108	-133 – -82	<0.001
Effect of type of TB (participants without signs of extrapulmonary TB vs those with signs of extrapulmonary TB)	35	-9 – 78	0.12
Effect of HIV viral load (per $\log_{10}$ cps/ml increase at screening)	-1	-2 – -1	<0.001
Effect of CD4 count (per increase of 10 CD4 cells/µl at screening)	-1	-3 – 2	0.48
Effect of previous tuberculosis	-26	-64 – 13	0.19
	Mean change in 6MWD from week 0	**95% CI**	**p-value**
Effect of time (visit)			<0.0001
week 4	-27	-50 – -4	
week 12	34	13 – 56	
week 28	69	48 – 91	
Effect of prophylactic prednisone			0.020
week 4	44	15 – 72	
week 12	-0.03	-27 – 27	
week 28	3	-23 – 30	

Change over time of forced expiratory volume in 1 second (FEV1) as % of predicted value

	FEV1 %	95% CI	p-value
Intercept (average FEV1 % if all other co-variates are 0)	80.7	65.9 – 95.5	
	Mean change in FEV1 %	**95% CI**	**p-value**
Effect of prednisone as treatment	1.5	-3.7 – 6.8	0.57
Effect of smoking (ever vs never)	-5.6	-10.3 - -0.8	0.022
Effect of age (per increase of one year in age at week 0)	0.06	-0.2 – 0.3	0.66
Effect of gender (female vs male)	-3.5	-8.8 – 1.9	0.21
Effect of type of TB (participants without signs of extrapulmonary TB vs those with signs of extrapulmonary TB)	0.7	-8.6 – 10.1	0.88
Effect of HIV viral load (per $\log_{10}$ cps/ml increase at	0.04	-0.1 – 0.2	0.64

screening)			
Effect of CD4 count (per increase of 10 CD4 cells/µl at screening)	-0.7	-1.3 – -0.2	0.008
Effect of previous tuberculosis	-14.8	-23.4 – -6.2	0.001

	Mean change in FEV1 % from week 0	**95% CI**	**p-value**
Effect of time (visit)			<0.0001
week 4	-1.5	-4.8 – 1.8	
week 12	2.9	-0.3 – 6.1	
week 28	6.4	3.1 – 9.6	
Effect of prophylactic prednisone			0.043
week 4	5.1	0.9 – 9.4	
week 12	-0.04	-4.1 – 4.0	
week 28	-1.0	-5.1 – 3.2	

Intercept and estimated coefficients with their 95% confidence intervals (95% CI) from the mixed effects regression models are listed. Data are adjusted for all other covariates presented in the table. We have not adjusted for TB-IRIS because we assume it to be on the causal pathway.

TABLE S4 The effect of baseline spirometry outcome on the effect of prednisone on change over time of forced expiratory volume in 1 second (FEV1) as % of predicted value

	FEV1 %	95% CI	
Intercept (average FEV1 % at week 0 for non-smokers with abnormal spirometry result)	67.1	63.4 - 70.8	<0.001
	Mean change in FEV1 %	**95% CI**	**p-value**
Effect of spirometry outcome at baseline (normal vs abnormal)	25.6	20.2 - 31.0	<0.001
Effect of smoking (ever vs never)	-2.0	-6.0 – 2.0	0.33
	Mean change in FEV1 % from week 0	**95% CI**	**p-value**
Effect of time (visit)			<0.0001
week 4	-0.3	-4.5 – 3.8	
week 12	4.3	0.4 – 8.2	
week 28	9.8	5.6 – 14.0	
Effect of prophylactic prednisone			0.12
week 4	5.9	0.7 – 11.2	
week 12	0.8	-4.5 – 6.0	
week 28	-0.4	-6.1 – 5.3	
Effect of normal spirometry at baseline			0.41
week 4	-0.4	-7.6 – 6.7	
week 12	-3.0	-10.5 – 4.5	
week 28	-6.7	-15.0 – 1.6	
Effect of normal spirometry at baseline on the effect of prophylactic prednisone			0.56
week 4	-5.3	-14.2 – 3.6	
week 12	-5.7	-15.0 – 3.7	
week 28	-3.3	-13.6 – 7.1	

Intercept and estimated coefficients with their 95% confidence intervals (95% CI) from the mixed effects regression models are listed. Data are adjusted for all other covariates presented in the table. Because allocation to either the prednisone or the placebo arm was randomized, no adjustment for baseline variables other than smoking and baseline spirometry outcome was done. Only participants with who had a baseline spirometry test done (n = 83) were included in this analysis.

TABLE S5 The effect of prednisone prophylaxis on change over time of forced vital capacity (FVC) as % of predicted value

	FVC %	95% CI	
Intercept (average FVC % at week 0 for non-smokers)	77.3	74.4 – 80.3	
	Mean change in FVC %	**95% CI**	**p-value**
Effect of smoking (ever vs never)	-5.0	-8.7 – -1.2	0.009
	Mean change in FVC % from week 0	**95% CI**	**p-value**
Effect of time (visit)			<0.0001
week 4	-0.8	-3.7 – 2.0	
week 12	4.3	1.6 – 7.0	
week 28	7.3	4.5 – 10.1	
Effect of prophylactic prednisone			0.015
week 4	4.9	1.3 – 8.5	
week 12	-0.1	-3.5 – 3.4	
week 28	-0.8	-4.4 –2.7	

Intercept and estimated coefficients with their 95% confidence intervals (95% CI) from the mixed effects regression models are listed. Data are adjusted for all other covariates presented in the table.

TABLE S6 The effect of tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) on change over time of forced vital capacity (FVC) as % of predicted value

	FVC %	95% CI	p-value
Intercept			
(average FVC % if all other co-variates are 0)	80.3	55.7 – 104.8	<0.001
	Mean change in FVC %	**95% CI**	**p-value**
Effect of TB-IRIS at week 0	2.9	-2.6 – 8.3	0.30
Effect of smoking (ever vs never)	-5.9	-10.1 – -1.6	0.007
Effect of age (per increase of one year in age at week 0)	0.1	-0.2 – 0.4	0.45
Effect of gender (female vs male)	-2.7	-7.8 – 2.3	0.29
Effect of type of TB (participants without signs of extrapulmonary TB vs those with signs of extrapulmonary TB)	3.7	-5.0 – 12.5	0.40
Effect of HIV viral load (per $\log_{10}$ cps/ml increase at screening)	-1.0	-4.6 – 2.7	0.61
Effect of CD4 count (per increase of 10 CD4 cells/µl at screening)	-0.7	-1.2 – -0.2	0.009
Effect of previous tuberculosis	-10.6	-18.7 – -2.6	0.010
	Mean change in FVC % from week 0	**95% CI**	**p-value**
Effect of time (visit)			<0.0001
week 4	1.7	-2.0 – 5.5	
week 12	7.5	3.9 – 11.0	
week 28	8.7	5.0 – 12.3	
Effect of TB-IRIS			0.026
week 4	-4.4	-8.5 – -0.4	
week 12	-5.7	-9.7 – -1.8	
week 28	-2.5	-6.7 – 1.7	
Effect of prophylactic prednisone			0.040
week 4	4.5	0.7 – 8.2	
week 12	-0.4	-4.0 – 3.1	
week 28	-0.8	-4.4 – 2.9	

Intercept and estimated coefficients with their 95% confidence intervals (95% CI) from the mixed effects regression models are listed. Data are adjusted for all other covariates presented in the table