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BRIEF REPORT

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

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End-organ impairment has received relatively little research attention as a possible manifestation of tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS). In this prospective cohort study, one-half of adults with human immunodeficiency virus and pulmonary tuberculosis experienced meaningful declines in lung function on antiretroviral therapy, suggesting a role for lung function in TB-IRIS definitions.

Keywords. tuberculosis; HIV; immune reconstitution inflammatory syndrome; pulmonary function.

Tuberculosis (TB) remains the number one cause of death of people with human immunodeficiency virus (HIV) [1]. Initiating antiretroviral therapy (ART) during TB treatment decreases mortality in adults with HIV and TB, but can trigger the immune reconstitution inflammatory syndrome (IRIS) [2]. Using standard clinical definitions, TB-IRIS is reported to occur in approximately 20% of those initiating ART during TB treatment, often involves the lungs, and is driven in part by immune restoration to mycobacterial antigens [2].

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Approximately one-half of HIV-negative adults cured of pulmonary TB have chronic lung impairment, and there is growing recognition of the global burden of respiratory disability following TB cure [3]. In people with HIV and TB coinfection, pulmonary inflammation from ART-mediated immune restoration may provoke additional lung damage, but there are limited data on lung function trajectories following ART initiation. Thus, we sought to determine the incidence of, risk factors for, and long-term impact of clinically meaningful lung function declines in adults initiating ART during TB treatment.

METHODS

We conducted a prospective cohort study enrolling ART-naive adults living with HIV with CD4 counts ≤500 cells/μL and GeneXpert-positive, rifampicin-susceptible pulmonary TB in Gauteng, South Africa, during 2016–2019. All participants initiated efavirenz, emtricitabine, and tenofovir during the intensive phase of short-course TB therapy. Lung function tests were conducted prior to (baseline) and at 4, 12, 24, and 48 weeks after ART initiation; participants completed at least 2 lung function tests in the first 12 weeks. Forced expiratory volume in 1 second (FEV_1) and forced vital capacity were measured with an EasyOne Pro Spirometer (ndd Medical Technologies, Andover, Massachusetts) as absolute volumes (mL) and percentage of predicted values (ie, referenced to age, sex, height, and race). Respiratory symptoms were assessed using the Chronic Obstructive Pulmonary Disease Assessment Test (CAT), and the 6-minute walk test (6MWT) was administered as a submaximal exercise test of pulmonary disability [4, 5]. CD4 count and HIV viral load were measured at baseline and week 4 of ART. Paradoxical TB-IRIS was identified at monthly visits using the Meintjes et al criteria [2].

We identified participants with an FEV_1 decline of ≥100 mL, the minimum clinically important difference in other pulmonary diseases [6], during the first 12 weeks after ART initiation. Those with a ≥100 mL decline were then divided into tertiles according to the amount of decline. We compared sociodemographic and clinical characteristics of participants with and without lung function declines using the χ^2 or Kruskal-Wallis test. Multivariate logistic regression was used to determine the association between an FEV_1 decline ≥100 mL in the first 12 weeks and impaired lung function at the end of TB treatment, which we defined as an FEV_1 <80% predicted at the latter available of the 24- or 48-week visit (ie, the "final" lung function measurement). We examined the following variables for effect modification or confounding: age, sex, smoking status, time to ART initiation, baseline CD4 count and viral load, and baseline $FEV_{1.}$ Covariates were included in the final model based on a priori knowledge or a bivariate association with final FEV_1 with a *P* value <.2. Analyses were conducted in SAS version 9.4 software (SAS Institute, Cary, North Carolina).

RESULTS

Participant sociodemographic and clinical characteristics are shown in Table 1. Among 101 participants with at least 2 lung function measurements in the first 12 weeks of ART, half (50 [50%]) had a clinically significant FEV_1 decline of at least 100 mL after ART initiation. After dividing those 50 participants into tertiles, 16 (16%) participants had a mild FEV_1 drop of 100–299 mL, 16 (16%) had a moderate drop of 300–599 mL, and 18 (18%) had a severe drop of ≥600 mL, with a median FEV_1 drop of 955 mL (interquartile range, 840–1240 mL) in these individuals. No participants had evidence of HIV treatment failure, and all successfully completed TB treatment.

An FEV_1 drop of at least 100 mL on ART was significantly associated with a longer 6MWT distance and higher FEV_1 at baseline, but not with other characteristics either at baseline or after ART initiation, including sputum culture status and time to culture positivity in liquid media (Table 1 and Figure 1). Although there was no significant difference in the final FEV_1 for those with and without lung function declines, a significantly greater proportion of those with severe declines (ie, FEV_1 drop ≥600 mL) had a final FEV_1 <80% predicted, compared with

Table 1. Clinical Characteristics According to the Presence or Absence of Pulmonary Immune Reconstitution Inflammatory Syndrome (IRIS) and Degree of Pulmonary IRIS

Characteristic[a]	No Lung Function Decline (n = 51)	Lung Function Decline (n = 50)	*P* Value[b]	Mild Lung Function Decline (n = 16)	Moderate Lung Function Decline (n = 16)	Severe Lung Function Decline (n = 18)
Baseline characteristics						
Age, y, mean (range)	36 (31–41)	36 (31–45)	> .5	36 (29–44)	36 (30–45)	36 (32–47)
Female sex	25 (49)	19 (38)	.26	8 (50)	7 (44)	4 (22)
Current smoker	5 (10)	10 (20)	.15	3 (19)	4 (25)	3 (17)
Time to ART initiation after TB treatment initiation, d	22 (16–38)	27 (15–47)	> .5	24 (16–32)	20 (14–47)	31 (23–49)
CD4 count, cells/µL	106 (48–204)	110 (51–182)	> .5	160 (66–274)	87 (20–133)	108 (51–180)
Log_{10} plasma HIV-1, copies/mL	5.1 (4.7–5.7)	5.3 (4.9–5.8)	.30	5.2 (4.8–5.5)	5.3 (5.0–5.7)	5.4 (5.0–5.8)
Sputum culture positive at baseline visit	24 (47)	21 (42)	> .5	7 (44)	7 (44)	7 (39)
Time to sputum culture positivity in liquid media among culture-positive samples, d	13 (9–15)	14 (12–18)	> .5	14 (12–16)	18 (13–18)	12 (9–17)
CAT score	5 (3–12)	5.5 (2–11)	.47	3 (1–11)	6.5 (1.5–9)	8 (4–12)
6MWT, m	368 (328–430)	408 (361–456)	**.05**	432 (362–479)	403 (312–456)	406 (368–449)
FEV_1 % predicted	71 (58–84)	82 (75–95)	**< .001**	81 (76–94)	86 (76–102)	82 (67–95)
FEV_1 <80% predicted	34 (67)	19 (38)	**.004**	6 (38)	5 (31)	8 (44)
Early change from baseline to 4 wk						
Increase in CD4 count, cells/µL	65 (26–106)	69 (25–172)	.36	51 (24–169)	79 (32–172)	64 (34–170)
Decrease in log VL	5.1 (4.7–5.6)	5.2 (4.7–5.6)	> .5	5.2 (4.6–5.5)	5.2 (4.6–5.5)	5.2 (4.9–5.7)
Change in CAT score	0 (−2 to 1)	0 (−1 to 2)	.44	0 (−1 to 1)	0.5 (−2.5 to 3.5)	−1 (−3 to 3)
Change in 6MWT, m	−12 (−48 to 22)	−27 (−60 to 7)	.19	−37 (−79 to 4)	−43 (−72 to −12)	−10 (−34 to 12)
Change in FEV_1, mL[c]	100 (−20 to 270)	−500 (−870 to −210)	**< .001**	−155 (−205 to −130)	−495 (−530 to −375)	−955 (−1240 to −850)
Final characteristics						
Final FEV_1 % predicted[d]	83 (68–90)	82 (73–93)	> .5	86 (77–92)	86 (77–100)	73 (67–83)
Final FEV_1 <80% predicted	15 (39)	20 (47)	> .5	5 (36)	5 (33)	10 (71)
Change in FEV_1, mL, baseline to final	400 (60–660)	−10 (−350 to 310)	**.01**	170 (−110 to 310)	0 (−190 to 230)	−375 (−540 to 580)

Mild pulmonary TB immune reconstitution inflammatory syndrome (IRIS) is defined as initial FEV_1 decline of 100-299 mL; moderate pulmonary TB-IRIS is defined as initial FEV_1 decline of 300-599 mL; and severe pulmonary TB-IRIS is defined as initial FEV_1 decline of ≥600 mL. *P* values ≤.05 are in bold.

Abbreviations: 6MWT, 6-minute walk test; ART, antiretroviral therapy; CAT, Chronic Obstructive Pulmonary Disease Assessment Test; FEV_1, forced expiratory volume in 1 second; HIV-1, human immunodeficiency virus type 1; TB, tuberculosis; VL, viral load.

[a]Unless otherwise indicated, continuous variables are expressed as median (interquartile range) and categorical variables are expressed as No. (%).

[b]*P* values compare those with and without pulmonary IRIS, using χ^2 test for categorical variables and Kruskal-Wallis test for continuous variables.

[c]Change in FEV_1 included change during baseline to 12 weeks, as explained in the Methods.

[d]Final values were available for 81 participants (38 no IRIS; 43 IRIS [14 mild, 15 moderate, 14 severe]) based on week 24 values for 30 participants and week 48 values for 51 participants.

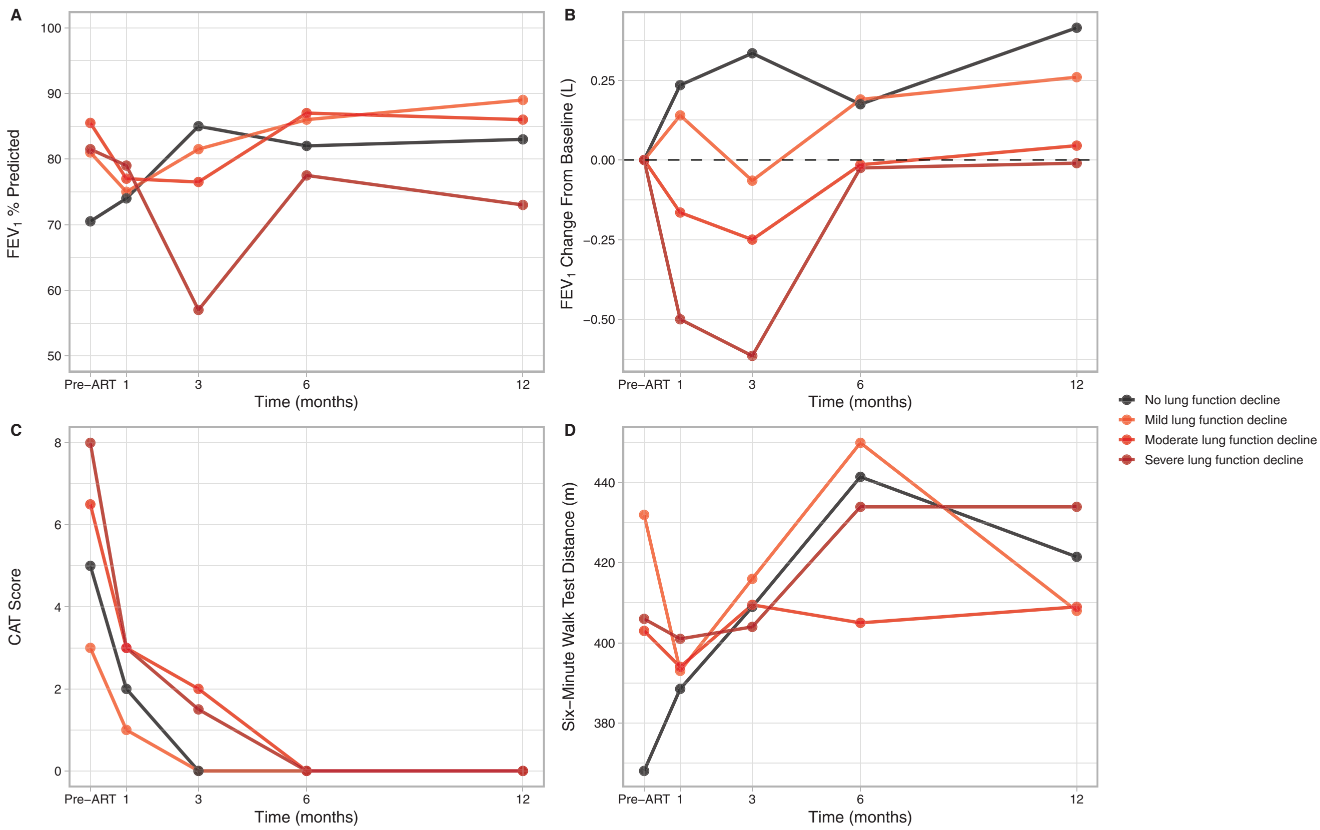

Figure 1. Lung function, pulmonary symptoms, and functional capacity over time. *A*, Predicted percentage of forced expiratory volume in 1 second (FEV_1). *B*, FEV_1 change from baseline. *C*, Chronic Obstructive Pulmonary Disease Assessment Test score. *D*, Six-minute walk test. Abbreviations: ART, antiretroviral therapy; CAT, Chronic Obstructive Pulmonary Disease Assessment Test; FEV_1, forced expiratory volume in 1 second.

those without a decline (71% vs 39%; P = .04). Furthermore, after adjustment for age, sex, time from TB treatment to ART initiation, baseline CD4 count, and baseline FEV_1, those with FEV_1 drops of any severity had >7 times the odds of having a final FEV_1 <80% predicted compared with those without an early FEV_1 drop (odds ratio, 7.59 [95% confidence interval, 1.67–34.63]). This significantly increased risk of a final FEV_1 <80% predicted seen after adjustment for baseline factors, notably the baseline FEV_1, parallels the trends in Figure 1A and 1B, whereby those who developed lung function declines typically started with higher lung function but had less recovery of lung function during treatment. All participants had improvements in their symptom scores, and most had accompanying improvements in their 6MWT.

Six participants met standard definitions for TB-IRIS [2], 5 of whom had qualifying spirometry. One had respiratory symptoms but did not experience a decline in lung function (Supplementary Table).

DISCUSSION

In this prospective cohort study, approximately half of those with pulmonary TB initiating ART experienced FEV_1 declines of a magnitude considered clinically significant in other pulmonary diseases [6], and 18% had severe FEV_1 drops associated with lung function that remained depressed at TB treatment completion, when impairment may be permanent [7]. These findings are important because decreased lung function is associated with increased mortality in people with and without overt pulmonary disease [8].

Patients whose lung function declined on ART experienced these declines within the first 3 months of ART initiation, completed TB treatment without evidence of microbiological failure, had no newly diagnosed pulmonary infections, and had substantial virologic decreases and CD4 increases on ART, consistent with standard definitions of paradoxical TB-IRIS [2, 9, 10]. Furthermore, the finding that less lung involvement at baseline was associated with an increased risk of lung function decline after starting ART is consistent with findings from a subset of this cohort, indicating that less pulmonary radiographic inflammation at baseline is associated with greater increases in lung inflammation during the initial weeks of ART [11]. Nonetheless, the lack of association between both bacterial burden and timing of ART initiation with declines in lung function contrasts with the concept that greater antigen burden drives TB-IRIS risk. Furthermore, TB progression despite TB treatment and ART initiation, drug toxicity, and undiagnosed pulmonary opportunistic illnesses cannot be excluded as possible contributors to the lung function declines we identified. Additional research is needed.

Lung function declines were not always symptomatic and may not be detected by routine TB-IRIS surveillance unless spirometry is performed. Our findings require validation, but suggest that otherwise unexplained drops in pulmonary function on ART warrant consideration as an additional criteria for a TB-IRIS diagnosis. In the definition used in this study, if lung function declines were considered "focal tissue involvement" (as per the Meintjes et al [2] definition), the incidence of IRIS would have increased considerably. Major lung function declines on ART could also be considered a manifestation of a "clinical course not consistent with the expected course of TB" to fulfill the definition of French et al [10], or could have spirometry added to radiography as a sign of worsening disease in the TB-IRIS–specific definition of Colebunders et al [9]. This functional definition of pulmonary TB-IRIS could help identify those experiencing incident pulmonary damage on ART [2]. Lung function declines of a magnitude associated with greater longer-term pulmonary impairment (eg, in this study, ≥600 mL) may merit a TB-IRIS diagnosis. Failure to improve from baseline, when acute TB-associated inflammation is present, to end of therapy was also common in this study and merits consideration as an IRIS criterion.

We were unable to conduct prediagnosis pulmonary function testing, nor did we have baseline and follow-up chest radiography. Our sample size also limits our ability to examine all risk factors of interest. Nevertheless, our data suggest that people with HIV and TB are at risk of incident lung damage following ART initiation. A recent randomized clinical trial demonstrated that corticosteroid use at the time of ART initiation decreased TB-IRIS risk in adults and that these or other anti-inflammatory therapies may improve pulmonary outcomes in this population [12]. Inhaled corticosteroids, which specifically target inflammation in the lungs, present another potential intervention. Preclinical data also indicate that novel agents, such as phosphodiesterase-4 and matrix metalloproteinase inhibitors, reduce lung involvement in small-animal models of TB [13, 14]. The majority of TB-related disease burden, as measured in disability-adjusted life-years, is due to pulmonary impairment after treatment completion [15]. Therefore, patients with HIV/TB may benefit from research on interventions to preserve lung function and prevent chronic pulmonary impairment on ART.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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