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RESEARCH

[18F]FDG PET and CT findings at therapy completion of pulmonary tuberculosis: comparison between HIV-positive and HIV-negative patients and impact on treatment response assessment

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Abstract

Background [18F]FDG-PET/CT is a sensitive non-invasive tool for assessing treatment response in patients with pulmonary tuberculosis. The data on the performance of [18F]FDG-PET/CT for response assessment among patients infected with the human immunodeficiency virus (HIV) is limited. Here, we investigated the differences between PET and CT lung findings on end-of-treatment [18F]FDG-PET/CT among HIV-positive versus HIV-negative patients who completed anti-tuberculous therapy for pulmonary tuberculosis.

Methods Patients who completed anti-tuberculous therapy for pulmonary tuberculosis and declared cured based on negative clinical and laboratory assessments for active pulmonary tuberculosis were prospectively recruited to undergo [18F]FDG-PET/CT. Patients were classified as having residual metabolic activity if PET metabolic activity was demonstrated in the lung parenchyma or complete metabolic response if there was no abnormally increased [18F]FDG avidity in the lungs and compared the CT features. We identified 10 CT lung changes, five were associated with active pulmonary tuberculosis (nodules, micronodules in tree-in-bud pattern, consolidation, pleural effusion, and [18F]FDG-avid mediastinal/hilar lymphadenopathy) and the rest were associated with inactive sequelae of prior pulmonary tuberculosis (cysts, cavities, fibrosis, bronchiectasis, and calcifications and compared their incidence between HIV-positive and HIV-negative patients.

Results Seventy-five patients were included with a mean age of 36.09 ± 10.49 years. There were fifty HIV-positive patients, all of whom were on antiretroviral therapy and with a median CD4 + T-cell of 255 cells/µL (IQR: 147–488). Fifteen HIV-positive patients had detectable HIV viremia with a median viral load of 12,497 copies/mL (IQR: 158–38,841). There was a significant difference in the incidence of residual metabolic activity and complete metabolic response between HIV-positive and HIV-negative patients. ($P = 0.003$) HIV-positive patients were more likely to have [18F]FDG-avid lymphadenopathy and HIV-negative patients had a higher incidence of cystic lung changes. The pattern of CT lung changes was otherwise not different between HIV-positive and HIV-negative patients. ($P > 0.05$)

Conclusions The incidence of residual metabolic activity and complete metabolic response on end-of-treatment [18F]F-FDG-PET/CT are similar between HIV-positive and HIV-negative patients. The incidence of [18F]FDG-avid mediastinal/hilar lymphadenopathy is more prevalent among HIV-positive patients. The pattern of lung changes was largely similar between HIV-positive and HIV-negative patients, indicating that the presence of HIV coinfection may not influence the interpretation of end-of-treatment [18F]F-FDG-PET/CT obtained for pulmonary tuberculosis treatment response assessment.

Keywords Pulmonary tuberculosis · [18F]FDG-PET/CT · Residual metabolic activity · Complete metabolic response · HIV infection

Extended author information available on the last page of the article

Introduction

Tuberculosis (TB) is still a major global health problem and one of the most widely distributed infectious diseases. Globally, the World Health Organisation (WHO) 2021, estimated about 10.6 million new cases and 1.6 million deaths worldwide from tuberculosis with the highest incidences in Africa and Asia [1]. Immunocompromised individuals with human immune deficiency virus (HIV) account for more than 50% of TB cases [2]. Co-infection of TB and HIV constitutes a major public health problem with increased morbidity and mortality [3].

Tuberculosis is treated with multiple drugs for a minimum of six months. At the completion of anti-tuberculous therapy, response is assessed by improvement in clinical symptoms and normalization of laboratory parameters. A negative sputum culture is the most definitive tool for response assessment following pulmonary tuberculosis treatment [4–6].

Unfortunately, some patients have negative sputum at the beginning of tuberculosis treatment [7], and a negative sputum culture at the end of anti-tuberculosis therapy is a less convincing indication of a cure. Culture also takes time, often requiring a couple of weeks for a positive culture to be obtained due to the slow-growing nature of *Mycobacterium tuberculosis* (MTb). [8–9] A need, therefore, exists for other robust biomarkers of sterilizing cure of TB.

[^{18}F]FDG-PET/CT is a valuable imaging technique in the management of infectious diseases including TB [10]. Emerging and evolving literature suggests that [^{18}F]FDG-PET/CT is clinically relevant in predicting response and evaluating treatment response during and after anti-tuberculous therapy. [11–12] Patients with residual metabolic activity in their lungs on end-of-treatment [^{18}F]FDG-PET/CT have a reasonable risk for TB relapse while complete metabolic response to anti-tuberculous therapy is consistent with a durable cure of pulmonary tuberculosis [13]. Recent evidence has emerged showing that patients declared cured based on a negative sputum culture but demonstrate residual metabolic activity on their end-of-treatment [^{18}F]FDG-PET/CT harbour live bacilli that are either dormant or slow-growing and at risk of disease relapse. [14–15] Lung findings on CT are useful for characterizing active and inactive lung infections such as TB. Our group has recently shown a good correlation between certain CT features suggestive of active pulmonary tuberculosis and the presence of residual metabolic activity associated with a risk of relapse on end-of-treatment [^{18}F]FDG-PET/CT [16].

HIV infection may present an additional challenge in during pulmonary tuberculosis treatment response assessment as it predisposes infected patients to other inflammatory and infectious co-morbid conditions that may result in pulmonary parenchyma sequelae difficult to distinguish from pulmonary tuberculosis-induced lung changes. Studies reporting the utility of end-of-treatment [^{18}F]FDG-PET/CT as a response assessment tool for pulmonary tuberculosis have included HIV-uninfected patients or unselected patient populations [12–14]. It remains unknown if the findings from these studies are applicable to the HIV-infected population. The determination of this is important considering the heightened risk of clinically overt TB in HIV-infected patients compared with those without HIV infection. We, therefore, investigated the differences in the incidence of residual metabolic activity and the pattern of CT lung findings on end-of-treatment [^{18}F]F-FDG-PET/CT among HIV-infected patients versus HIV-uninfected patients who completed a standard course of anti-tuberculous therapy for pulmonary tuberculosis.

Patients & methods

Patients

This is a secondary analysis of a prospective cohort study. Approval of this study was granted by the human research ethics committees at the University of Pretoria and Sefako Makgatho Health Sciences University.

Based on the standard of care as per the South African guidelines [17], patients who were considered cured of pulmonary tuberculosis were prospectively recruited to undergo [^{18}F] FDG-PET/CT imaging between December 2017 and September 2021. All patients completed their [^{18}F]FDG-PET/CT within two weeks of completing anti-tuberculous therapy.

We included patients aged 16-65years with microbiologically confirmed drug-sensitive pulmonary tuberculosis (DS-PTB) who completed a full course of anti-tuberculous therapy and declared cured without the need for further treatment(as deemed by the primary clinician and per the South African guidelines for PTB management), with known HIV status, and culture-confirmed TB susceptible to first-line tuberculosis drugs and positive GeneXpert (Cepheid) at the beginning of treatment were considered eligible for this study.

Exclusion criteria included those with unknown HIV status, previous tuberculosis treatment, culture, and GeneXpert positive sputum at the end of treatment, previous tuberculosis treatment within 3 years of present infection, any recorded evidence of drug-resistant tuberculosis, malignancy and signs and symptoms of acute illness, receipt of non-standard, incomplete or investigational TB regimen, receipt of any investigational products or investigational drug in the past 6 months or investigational vaccine ever, disease condition requiring receipt of systemic steroids or

other immunosuppressive medications in the preceding 6 months, pregnancy or breastfeeding, anemia (hemoglobin, < 7 g/dL), significant smoking history (> 30 pack-years) and uncontrolled diabetes mellitus. Written informed consent was obtained from the study participants.

Before study entry, all patients had a comprehensive clinical assessment, including clinical history and physical examination for signs and symptoms of pulmonary tuberculosis. All patients also had HIV screening, sputum microscopy for acid-fast bacilli, GeneXpert/RIF (Cepheid), drug sensitivity and culture testing, and urinary pregnancy testing for women of child-bearing potential. Only patients who had negative signs and symptoms screening and negative laboratory assessment for pulmonary tuberculosis were scheduled for [^{18}F]FDG PET/CT.

[^{18}F] -FDG PET/CT imaging

Study participants underwent imaging with [^{18}F] -FDG PET/CT performed within 14 days following completion of therapy at the Department of Nuclear Medicine, Steve Biko Academic Hospital, the University of Pretoria. Patients were made to fast for a minimum of four hours and a fasting blood glucose < 7mmol/L was a prerequisite to proceed with the [^{18}F]FDG-PET/CT. A weight-based formula was used to calculate the activity of [^{18}F] -FDG administered: [(body weight /10) + 1] x 37 MBq. Data acquisition (unenhanced CT scan followed by PET imaging) was performed on a Siemens Biograph 40 true point hybrid PET/CT dedicated system, 1 h after tracer injection. Patients were scanned from vertex to mid-thigh. Images were acquired in 3-dimensional mode at 3 min per-bed position and reconstructed with and without attenuation correction (CT-based) using ordered-subset expectation maximization yielding axial, sagittal, and coronal slices.

Image interpretation and analysis

A dedicated workstation equipped with Syngo.Via software (Siemens Medical Solutions) was used to interpret and analyse [^{18}F]FDG-PET/CT images. [^{18}F]FDG-PET/CT images were reviewed in all 3 planes as well as MIP views. The PET/CT scan was interpreted independently by two experienced nuclear medicine physicians and disagreements were resolved by discussion in a consensus discussion by the two nuclear medicine physicians.

CT image analysis

The presence of features of active tuberculosis versus residual lung damage due to TB in the lungs of the patients was assessed on the [^{18}F]FDG-PET/CT images. The following lesions were considered suggestive of active tuberculosis; lung nodules, lung consolidation, micronodules in the tree-in-bud pattern, cavitary lung lesions with [^{18}F]FDG avidity in its wall, [^{18}F]FDG -avid thoracic lymph nodes, and pleural effusion. Cystic lung findings, cavitary pulmonary lesions without [^{18}F]FDG avidity in its wall, bronchiectetic findings, calcification, and fibrotic lung findings all demonstrating no[^{18}F]FDG avidity were considered suggestive of inactive lung findings to previous PTB disease.

18 F-FDG PET image analysis

Qualitative assessment entailed interpreting [^{18}F]FDG uptake against a common background, in this case, the mediastinum. Any focal enhanced [^{18}F]FDG uptake in the lung parenchyma above the mediastinal background activity was considered significant residual metabolic activity after treatment. Patients were subsequently categorised into two groups; the residual metabolic activity group if there is a presence of significant residual metabolic activity on the end-of-treatment [^{18}F]FDG-PET/CT and the non-residual metabolic activity group if there was no significant residual metabolic activity, meaning they had a complete metabolic response to anti-tuberculous therapy.

Statistical analysis

Statistical analysis was performed using IBM SPSS statistic version 21.0(IBM Corp.Armond New York USA, Descriptive statistics of baseline clinical and demographic information as absolute and relative frequencies, mean, and standard deviation (SD) were used to characterise the study population. An unpaired t-test or a x2 test was used to compare the differences in the variables of patients who achieved complete metabolic response (CMR) to anti-tuberculous therapy compared with patients who had residual metabolic activity at the end of treatment for pulmonary tuberculosis amongst those with HIV and non-HIV patients, depending on whether the parameters were discrete or continuous variables, respectively. Statistical significance was set at a p value of less than 0.05.

Results

Patient characteristics

Overall, 75 patients including 28 females (33.33%) and 47 males (62.67%); with a mean age of 36.09 ± 10.49 constituted the study population. The mean Body-Mass Index (BMI) and hemoglobin level of the study population were 21.88 ± 5.90 kg/m^2 and 13.41 ± 1.93, g/respectively, The

median CRP level was 4.31 mg/l. Of the study participants, 25 (333%) were smokers with smoking history of less than 30 pack years.

Fifty participants (66.67%) were HIV-positive with a median CD4 T cell count of 255 (IQR = 147–448) cells/μL. All the 50 HIV-positive patients were on antiretroviral therapy (ART). Among the HIV-infected patients, 35 (70.00%) patients had achieved a completely suppressed viremia while detectable HIV viremia was seen in 15 patients (median HIV viral load = 12, 497 copies/mL) at the time of EOT [^{18}F]FDG-PET/CT scan. Table 1 shows the detailed baseline clinic characteristics of the participants.

[^{18}F]-FDG PET pulmonary findings after pulmonary tuberculosis treatment

All study participants completed an end-of-treatment [^{18}F]FDG-PET/CT. Forty-one patients (54.7%) had residual metabolic activity, and 34 patients (45.3%) achieved a complete metabolic response after anti-tuberculous therapy. Of the HIV-positive individuals, 24 had residual metabolic activity, while 26 achieved complete metabolic response. Likewise, 17 patients without HIV infection demonstrated residual metabolic activity, while 8 achieved complete metabolic response. The difference in the prevalence of residual metabolic activity in patients with HIV-positive infection versus those without HIV infection was not statistically significant. Also, the prevalence of complete metabolic response did not differ significantly between those with HIV infection compared to those without HIV infection Figs. 1, 2 and 3 for patients with complete metabolic response and residual metabolic activity.

Patients with residual metabolic activity on their end-of-treatment [^{18}F]FDG-PET/CT were significantly more likely to be older than 45 years(12(80%), $p = 0.028$). Among the HIV-infected patients, those with CD4 + T-cell count of above200 cells/μL and undetectable HIV viremia were more likely to have residual metabolic activity compared with HIV-infected patients who had low CD4 + T-cell below 200 cells/μL and a detectable level of HIV viremia (Table 2). Other parameters including, gender, BMI, hemoglobin levels, CRP levels, and HIV positivity, were not significantly different between patients with residual metabolic activity versus those without.

Table 1 Demographic and clinical characteristics of the study participants

Variable	Frequency	Percent
Age		
< 45	60	80.0
≥ 45	15	20.0
Mean ± SD	36.09 ± 10.49	
Range	20–65	
Gender		
Male	47	62.7
Female	28	37.3
HIV		
Yes	50	66.7
No	25	33.3
CD4 T cell count (cells/μL)		
Median (IQR)	255 (147–448)	
HIV viral load (copies/mL)		
Detectable	15	30.0
Not detectable	35	70.0
Viral load (detectable)		
Median (IQR)	12497.00 (158.00–38841.00)	
Smoking		
Yes	25	33.3
No	50	66.7
BMI (kg/m^2)		
Mean ± SD	21.88 ± 5.90	
Range	15.19–48.15	
Haemoglobin (g/dL)		
Mean ± SD	13.41 ± 1.93	
Range	8.80–17.00	
CRP (mg/L)		
Median (IQR)	4.31 (1.36–11.06)	

HIV: Human Immunodeficiency Virus; CD4: Cluster of Differentiation 4; BMI: Body Mass Index; CRP: C-Reactive Protein

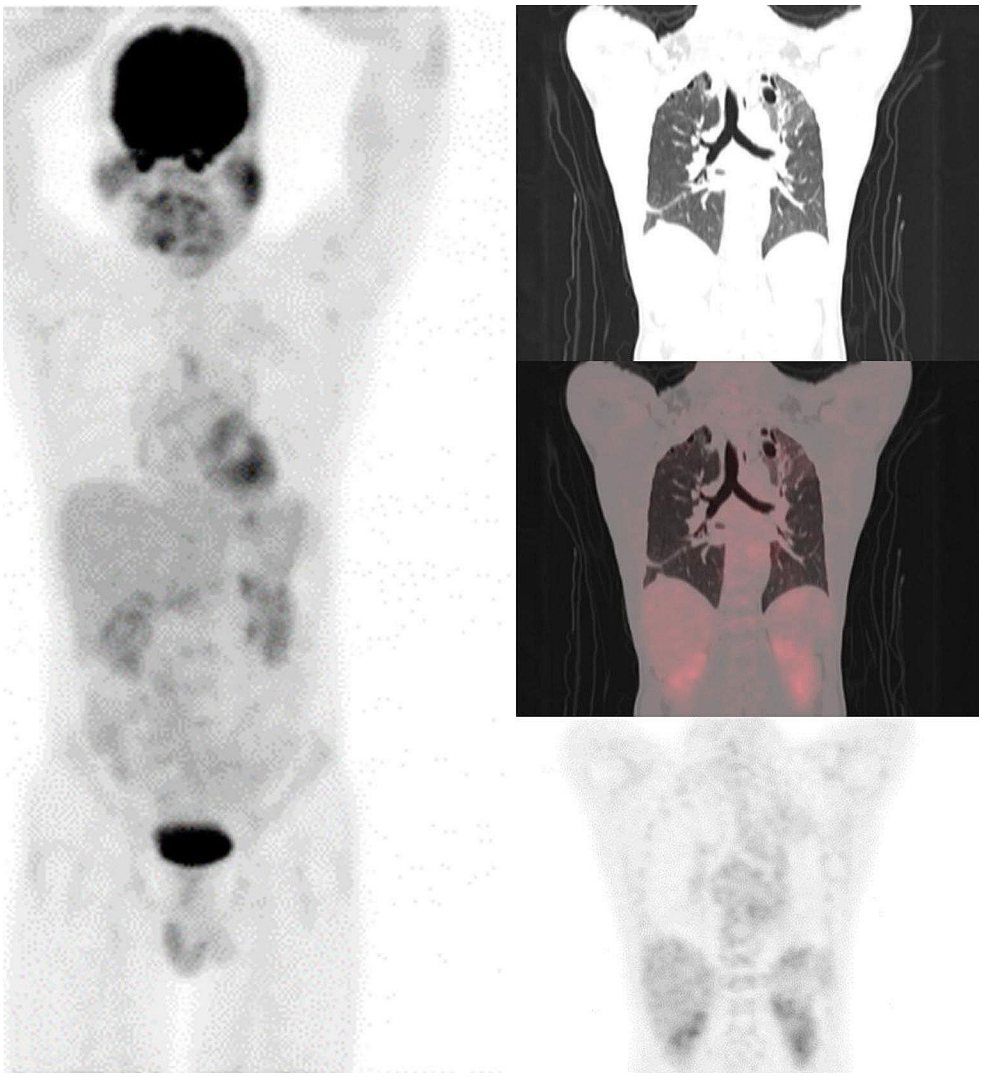

Fig. 1 A 37-year-old male with HIV infection who completed a six-month course of anti-tuberculous therapy for drug-sensitive pulmonary tuberculosis. The maximum intensity projection(MIP) and the axial (from top-to bottom) CT, fused PET/CT, and corrected PET demonstrated bilateral fibro-cavitatory lung changes most notably involving the upper lobes without corresponding significant residual metabolic activity(RMA)

Among the patients who attained complete metabolic response on their end-of-treatment ^{18}F-FDG-PET/CT, HIV-infected patients were more likely to be older than those patients without HIV infection (36.69 ± 8.04 years versus 27.75 ± 9.21, $p = 0.012$). The CRP level was also significantly higher among HIV-infected patients who achieved complete metabolic response compared to HIV-uninfected patients who achieved complete metabolic response (4.10 versus 0.89, $p = 0.010$). BMI and hemoglobin levels were not significantly different between HIV-positive patients who achieved complete metabolic activity on PET after anti-tuberculous treatment versus HIV-negative patients who attained complete metabolic response at the end of anti-tuberculous therapy, (Table 3).

CT lung findings after pulmonary tuberculosis treatment

Of the lung findings of markers of active TB, lung nodules were most prevalent ($n = 53$) while pleural effusion was the least prevalent ($n = 2$). Likewise, fibrotic lung lesions constituted the most prevalent lung findings of inactive disease, with calcification being the least prevalent marker of inactive disease. Furthermore, most patients had mixed (findings ascribable to both active and inactive TB) lung findings on CT with 59 patients (78.67%) having bilateral lung findings on CT(Table 4).

CT lung findings among patients with residual metabolic activity: HIV-positive versus HIV-negative patients

Overall, 29 patients with RMA had CT features of active pulmonary tuberculosis disease, 17 were HIV-positive patients

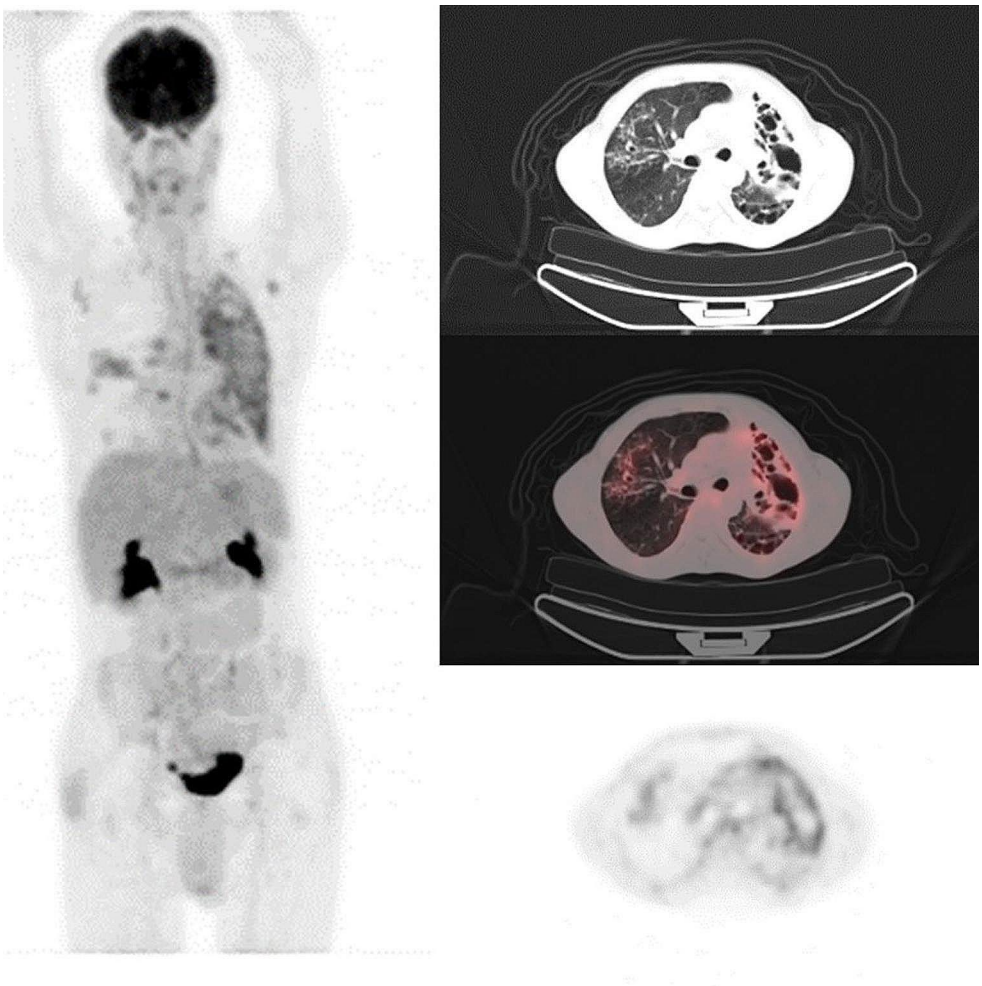

Fig. 2 A 40-year-old female known with HIV infection who completed a six-month course of anti-tuberculous therapy for drug-sensitive pulmonary tuberculosis. The maximum intensity projection (MIP) and axial(from top to bottom) CT, and fused PET/CT and attenuation corrected PET images demonstrate residual metabolic in the tree in bud appearance and lung nodules in the right middle lobe and bronchiectasis involving the left lobe

and 12 were HIV-negative patients. No CT lung changes suggestive of active pulmonary tuberculosis were seen in 12 patients, seven of whom were HIV-positive while five of them were HIV-negative. There was no significant association between the presence or absence of active CT lung findings and the presence of residual metabolic activity. In total, 35 patients had CT lung changes of inactive disease; 17 of them were HIV positive and 12 of them were HIV-negative. Six patients had none of the CT features of inactive pulmonary tuberculosis; five of them were HIV-positive while one patient was HIV-negative. The relationship between the presence or absence of CT lung findings of inactive disease with the presence of residual metabolic activity was not significantly different between HIV-positive and HIV-negative patients (Table 5).

We further investigated the differences in the incidence of the individual CT lung findings and their association with residual metabolic activity between HIV-positive and HIV-negative patients. Cystic lung findings, a manifestation of inactive change induced by prior PTB, were significantly more prevalent among HIV-negative compared with HIV-positive patients. Conversely, [^{18}F]FDG-avid mediastinal or hilar lymph nodes were more likely seen in HIV-positive patients (seen in 50.0% of patients) compared with HIV-negative patients (seen in 5.9% of patients). The other individual CT lung findings were not significantly different between HIV-positive and HIV-negative patients who had residual metabolic activity on their end-of-treatment [^{18}F] FDG-PET/CT scan (Table 5).

CT lung findings among patients with complete metabolic response: HIV-positive versus HIV-negative patients

Among patients who had a complete metabolic response on [^{18}F]FDG PET, 24 of them had at least one of the CT lung findings suggestive of inactive pulmonary tuberculosis, 18 of whom were HIV-positive while six of them were HIV-negative. None of the CT lung findings suggestive of inactive pulmonary tuberculosis was seen in 10 patients, eight of whom were HIV-positive and two were HIV-negative. There were no significant differences in the distribution of CT findings of inactive pulmonary tuberculosis among the HIV-positive and HIV-negative patients. CT findings of

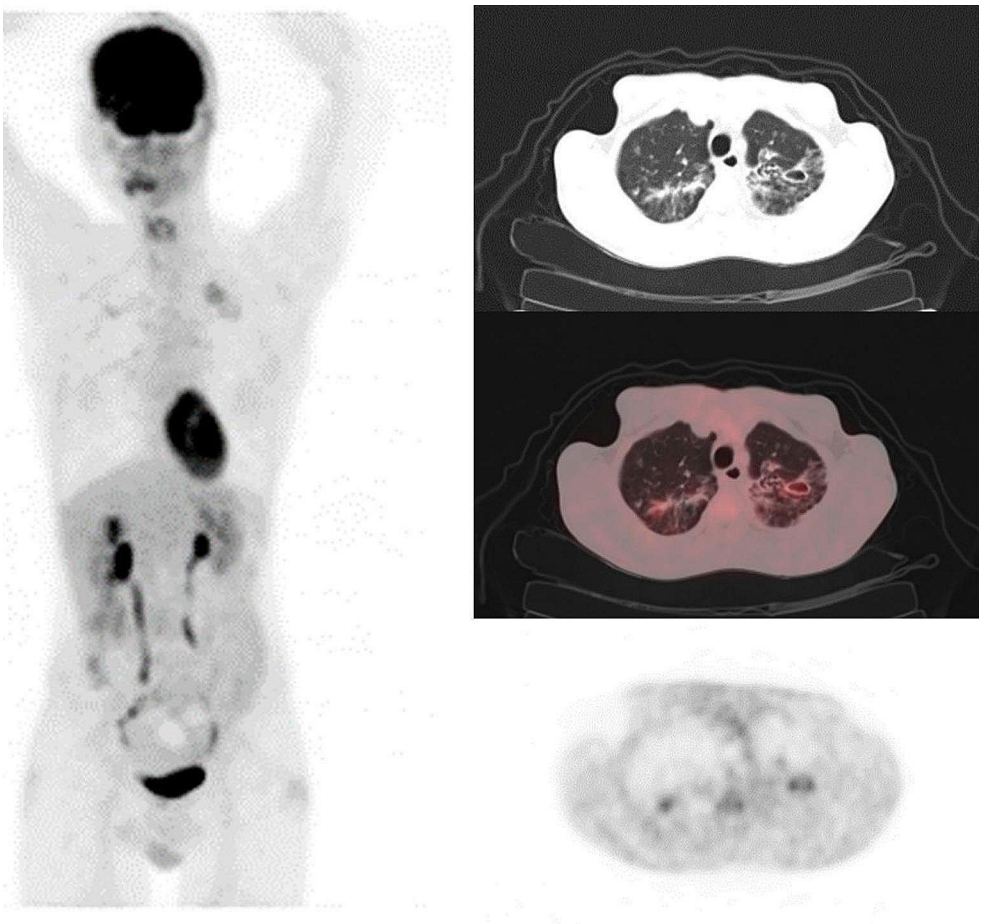

Fig. 3 A 37-year-old male with no history of HIV infection post-treatment for drug-sensitive pulmonary tuberculosis. The maximum intensity projection (MIP) and axial (from top to bottom) CT, and fused PET/CT and attenuation corrected PET images show bilateral residual metabolic activity (RMA) in the lungs, involving the upper lobes, left more than right

active pulmonary tuberculosis were rare among the patients who attained complete metabolic response on their EOT [^{18}F]FDG PET, seen only in three patients (two HIV-positive and one HIV-negative). None of the individual CT lung findings demonstrated any significant differences in their distribution between HIV-positive patients and HIV-negative patients (Table 6). Figures 1, 2 and 3 show the typical imaging findings in our study population.

Discussion

In this study, we performed a comparative analysis of the CT lung findings in patients with or without HIV infection who completed a standard course of ATT for pulmonary tuberculosis and were declared cured based on the current standard of care. We found a significant association between residual metabolic activity and certain CT lung findings on end-of-treatment [^{18}F]FDG-PET/CT [16]. In a cohort of 75 prospectively recruited patients, including 50 HIV-positive patients, HIV-positive patients were significantly older and had higher serum CRP levels than HIV-negative patients. The [^{18}F]FDG PET/CT findings were not significantly different between HIV-positive and HIV-negative patients. However, among HIV-positive patients, we found a higher incidence of residual metabolic activity in patients who had CD + T-cell count ≥ 200 cells/μL and without detectable HIV viremia compared with patients with CD + T-cell count below 200 cells/μL and detectable HIV viremia. Our group and others have previously reported a high incidence of residual metabolic activity on end-of-treatment [18F] FDG-PET/CT and its association with an increased risk of TB relapse in patients who completed a standard course of anti-tuberculous therapy. [13–14]Among the patients with residual metabolic activity, cystic lung findings were more prevalent among HIV-positive patients compared with HIV-negative patients. Conversely, [^{18}F]FDG-avid mediastinal/hilar lymphadenopathy was more common among HIV-positive patients compared with HIV-negative patients, despite the challenges of adequately assessing lymph nodes on non-contrast enhanced CT. Interestingly, among patients achieved complete metabolic response on their end-of-treatment [^{18}F]FDG-PET/CT, CT findings suggestive of active pulmonary tuberculosis was very rare and there was high concordance in the prevalence of CT lung findings due to inactive disease between HIV-positive and HIV-negative.

Table 2 Comparison of baseline clinical and demographic characteristics between patients with residual metabolic activity and those with complete metabolic response on end-of-treatment [^{18}F]FDG-PET/CT

	Residual metabolic activity					
	Yes	No	Total	OR (95% CI)	χ^2	*p* value
Variable	*n* = 41(%)	*n* = 34(%)	*N*			
Age						
< 45	29 (48.3)	31(51.7)	60	0.234 (0.060–0.914)	4.856	**0.028***
≥ 45	12 (80.0)	3 (20.0)	15			
Gender						
Male	25 (53.2)	22 (46.8)	47	0.852 (0.332–2.187)	0.111	0.740
Female	16 (57.1)	12 (42.9)	28			
BMI (kg/m^2)						
< 18.5	15 (62.5)	9 (37.5)	24	1.603 (0.594–4.322)	0.874	0.350
≥ 18.5	26 (51.0)	25 (49.0)	51			
Hb level (g/dL)						
< 12	12 (75.0)	4 (25.0)	16	2.889 (0.825–10.116)	2.894	0.089
≥ 12	27 (50.9)	26 (49.1)	53			
CRP level (mg/dL)						
< 10	26 (53.1)	23 (46.9)	49	0.609 (0.207–1.786)	0.824	0.364
≥ 10	13 (65.0)	7 (35.0)	20			
HIV						
Yes	24 (48.0)	26 (52.0)	50	0.434 (0.159–1.189)	2.690	0.101
No	17 (68.0)	8 (32.0)	25			
CD4 T cell count (cells/µL)						
< 200	4 (20.0)	16 (80.0)	20	0.139 (0.036–0.531)	9.216	**0.002***
≥ 200	18 (64.3)	10 (35.7)	28			
HIV viral load (copies/mL)						
Detectable	3 (20.0)	12 (80.0)	15	0.167 (0.040–0.700)	6.731	**0.009***
Not detectable	21 (60.0)	14 (40.0)	35			

*χ2, Chi square test; OR, Odds ratio; 95% CI, 95% Confidence Interval; *p-value < 0.05; BMI, Body Mass Index; Hb, Hemoglobin; CRP, C-Reactive Protein; CD4, Cluster of Differentiation; HIV, Human Immunodeficiency Virus Infection*

Table 3 Comparison of the clinical and demographic characteristics of HIV-positive versus HIV-negative patients

	HIV				
	Positive	Negative	Total	χ^2	*p* value
Variable	*n* (%)	*n* (%)	*N* (%)		
Age					
Mean ± SD	36.69 ± 8.04	27.75 ± 9.21		2.662 ^{t}	**0.012**
Gender					
Male	16 (61.5)	6 (75.0)	22 (64.7)	0.485^{F}	0.681
Female	10 (38.5)	2 (25.0)	12 (35.3)		
BMI (kg/m^2)					
Mean ± SD	23.32 ± 6.79	22.19 ± 5.32		0.433 ^{t}	0.668
Hb (g/dl)					
Mean ± SD	13.35 ± 1.72	15.15 ± 1.94		-1.928 ^{t}	0.064
CRP (mg/dl)					
Median (IQR)	4.10 (1.89–11.40)	0.89 (0.37–1.26)		9.500 ^{U}	**0.010**

*χ2, Chi square test; OR, Odds ratio; 95% CI, 95% Confidence Interval; *p-value < 0.05; BMI, Body Mass Index; Hb, Hemoglobin; CRP, C-Reactive Protein; CD4, Cluster of Differentiation; HIV, Human Immunodeficiency Virus Infection*

HIV infection increases the risk of acquiring new MTb infection, its progression to clinical pulmonary tuberculosis disease, and the reactivation of latent TB infection [10, 18]. [^{18}F]FDG-PET/CT is a useful non-invasive tool for PTB treatment response assessment as it demonstrates residual metabolic activity in patients who still harbour MTb [11, 18–21]. Despite the known clinical utility of [18F]FDG PET/CT in PTB, there is limited published data reporting the differences in the lung findings among HIV-positive patients compared to HIV-negative patients at the end of

Table 4 Summary of findings on end-of-treatment FDG PET/CT scans

Variable	Frequency	Percent
Residual metabolic activity		
Yes	41	54.7
No	34	45.3
CT findings		
Bilateral lung changes	59	78.7
Cavity	30	40.0
Cyst	14	18.7
Nodules	53	70.7
Consolidation	10	13.3
Bronchiectasis	35	46.7
Calcification	5	6.7
Fibrotic changes	55	73.3
Tree-in-bud pattern	29	38.7
Mediastinal/hilar nodes	17	22.7
Pleural effusion	2	2.7

treatment for pulmonary tuberculosis. The pattern of lung changes, either due to the PTB or other lung diseases, is a significant confounder in the interpretation of end-of-treatment [^{18}F]FDG PET/CT [11, 16]. A major finding from this study is the low incidence of any of the CT lung changes suggestive of active pulmonary tuberculosis among patients who achieved complete metabolic response on their end-of-treatment [^{18}F]FDG-PET/CT. This is in agreement with the results from our previous study and suggests a good correlation between [^{18}F]FDG PET and CT findings in patients assessed for pulmonary tuberculosis treatment response [16]. A negative [^{18}F]FDG PET is predictive of sterilizing cure as no patient with a negative PET finding experienced relapse during follow-up in a previously published series [13].

Since [^{18}F]FDG PET/CT is not as readily available for pulmonary tuberculosis response assessment compared with stand-alone CT, our findings support the utility of stand-alone CT for this indication. This indication is valid both for HIV-positive and HIV-negative patients as there was no significant difference in the pattern of CT lung findings between HIV-positive and HIV-negative patients provided they achieved CMR on their end-of-treatment [^{18}F]FDG-PET/CT.

Among patients who had RMA on their EOT [^{18}F]FDG-PET/CT, [18F]FDG-avid mediastinal/hilar lymph nodes were more prevalent in HIV-positive patients compared with HIV-negative patients. This is no surprising and is consistent with the generalized lymphadenopathy known to be induced by HIV infection [22–25]. The pattern of HIV-induced lymphadenopathy and the level of [^{18}F]FDG avidity is a function of the disease severity [18, 22, 25]. Patients with advanced HIV infection characterized by low CD4 + T-cell count and a high HIV viral load have more widespread lymphadenopathy with involvement of the hilar and mediastinal lymph nodes as well as intense [^{18}F]FDG avidity in the enlarged node [18, 22, 25]. In our study cohort, in addition to a higher incidence of [^{18}F]-FDG-avid mediastinal/hilar lymphadenopathy among HIV-positive patients, HIV-positive patients with lower CD + T-cell count and detectable HIV viremia had a significantly higher chance of residual metabolic activity at the completion of PTB. Put together, these suggest that there is a higher chance of abnormal PET abnormalities both in the lung parenchyma and the draining lymph node basin among HIV-positive patients with sub-optimal disease control by anti-retroviral therapy. All HIV-positive patients included in this series were on stable anti-retroviral therapy, though about a third of them still had detectable HIV viremia at the time of PET/CT imaging. Cystic lung findings but not cavitatory lung findings were more prevalent among HIV-negative patients compared with HIV-positive patients. This cause warrants further studies to determine the aetiopathogenesis. Despite these, on a group level, both CT lung findings and PET findings were not significantly different between HIV-positive and HIV-negative patients. This, therefore, suggests that [^{18}F]FDG-PET/CT will have comparable performance when applied for PTB treatment response among HIV-positive patients compared with HIV-negative patients. It is safe also to assume that the robust published data on the utility of [18F]FDG-PET/CT for PTB response assessment in HIV-negative patients and mixed patient populations can be applied to HIV-positive patients as well.

Our study has many strengths, including the study population and its prospective design. Published data on [^{18}F]FDG-PET/CT imaging of pulmonary tuberculosis are limited by the small study populations and the retrospective study design. The prospective design of our study allowed for meticulous patient selection and rigorous clinical and laboratory assessments before study entry. All patients

Table 5 Comparison of the prevalence of CT lung changes between HIV-positive patients with residual metabolic activity and HIV-negative patients with residual metabolic activity on their end-of-treatment PET/CT

	HIV					
	Positive	Negative	Total	OR (95% CI)	χ^2	*p* value
Variable	*n*(%)	*n*(%)	*N*			
Cavity						
Yes	14 (58.3)	8 (47.1)	22 (53.7)	1.575 (0.451–5.504)	0.509	0.476
No	10 (41.7)	9 (52.9)	19 (46.3)			
Cyst						
Yes	1 (4.2)	6 (35.3)	7 (17.1)	0.080 (0.09–0.745)	6.810[F]	**0.014**
No	23 (95.8)	11 (64.7)	34 (82.9)			
Nodules						
Yes	22 (91.7)	15 (88.2)	37 (90.2)	1.467 (0.186–11.587)	0.133[F]	1.000
No	2 (8.3)	2 (11.8)	4 (9.8)			
Consolidation						
Yes	6 (25.0)	3 (17.6)	9 (22.0)	1.556 (0.330–7.343)	0.314[F]	0.711
No	18 (75.0)	14 (82.4)	32 (78.0)			
Bronchiectasis						
Yes	13 (54.2)	11 (64.7)	24 (58.5)	0.645 (0.180–2.315)	0.455	0.500
No	11 (45.8)	6 (35.3)	17 (41.5)			
Calcification						
Yes	1 (4.2)	2 (11.8)	3 (7.3)	0.326 (0.027–3.921)	0.847[F]	0.560
No	23 (95.8)	15 (88.2)	38 (92.7)			
Fibrotic changes						
Yes	17 (70.8)	15 (88.2)	32 (78.0)	0.324 (0.058–1.805)	1.759[F]	0.262
No	7 (29.2)	2 (11.8)	9 (22.0)			
Tree-in -bud						
Yes	15 (62.5)	12 (70.6)	27 (65.9)	0.694 (0.183–2.628)	0.290	0.591
No	9 (37.5)	5 (29.4)	14 (34.1)			
Nodes						
Yes	12 (50.0)	1 (5.9)	13 (31.7)	16.000 (1.821–140.549)	8.945	**0.003**
No	12 (50.0)	16 (94.1)	28 (68.3)			
Pleural effusion						
Yes	1 (4.2)	1 (5.9)	2 (4.9)	0.696 (0.040–11.958)	0.063[F]	1.000
No	23 (95.8)	16 (94.1)	39 (95.1)			
Bilateral disease						
Yes	21 (87.5)	14 (82.4)	35 (85.4)	1.500 (0.264–8.523)	0.211[F]	0.679
No	3 (12.5)	3 (17.6)	6 (14.6)			
CT inactive disease						
Yes	19 (79.2)	16 (94.1)	35 (85.4)	0.238 (0.025–2.248)	1.781[F]	0.373
No	5 (20.8)	1 (5.9)	6 (14.6)			
CT active disease						
Yes	17 (70.8)	12 (70.6)	29 (70.7)	1.012 (0.258–3.962)	0.000[F]	1.000
No	7 (29.2)	5 (29.4)	12 (29.3)			

*χ2, Chi square test; OR, Odds ratio; 95% CI, 95% Confidence Interval; *p-value < 0.05; CT, Computed Tomography; F, ANOVA (Analysis of Variance)*

completed a standard course of anti-tuberculous therapy and had their [^{18}F]FDG-PET/CT within two weeks of treatment completion. Our study has some important limitations at the same time, the most important being the lack of follow-up data to investigate further the impact of PET and CT findings on the risk of tuberculosis relapse. While residual metabolic activity at anti-tuberculosis therapy completion is associated with an increased risk of TB relapse, the rate of relapse is generally low [13]. Residual metabolic activity seen on end-of-treatment [^{18}F]FDG-PET/CT may be due to sterile inflammation induced by dead bacilli or due to slow-growing, non-culturable bacilli. [11, 13–14] These bacilli are not only fastidious in culture but difficult to obtain from biological sample, often requiring invasive procedures such as bronchoalveolar lavage to obtain suitable biological sampling [11, 13–15]. The non-specificity of residual metabolic activity on 18F-FDG PET/CT scan poses a significant challenge as FDG targets inflammation. Therefore, tracers

Table 6 Comparison of the prevalence of CT lung changes between HIV-positive patients with complete metabolic response and HIV-negative patients with complete metabolic response on their end-of-treatment PET/CT

	HIV					
	Positive	Negative	Total	OR (95% CI)	χ^2	*p* value
Variable	*n*(%)	*n*(%)	*N*			
Cavity						
Yes	5 (19.2)	3 (37.5)	8 (23.5)	0.397 (0.070–2.243)	1.135[F]	0.355
No	21 (80.8)	5 (62.5)	26 (76.5)			
Cyst						
Yes	6 (23.1)	1 (12.5)	7 (20.6)	2.100 (0.214–20.640)	0.419[F]	1.000
No	20 (76.9)	7 (87.5)	27 (79.4)			
Nodules						
Yes	12 (46.2)	4 (50.0)	16 (47.1)	0.857 (0.176–4.186)	0.036[F]	1.000
No	14 (53.8)	4 (50.0)	18 (52.9)			
Consolidation						
Yes	1 (3.8)	0 (0.0)	1 (2.9)		0.317[F]	1.000
No	25 (96.2)	8 (100.0)	33 (97.1)			
Bronchiectasis						
Yes	7 (26.9)	4 (50.0)	11 (32.4)	0.368 (0.072–1.889)	1.489[F]	0.388
No	19 (73.1)	4 (50.0)	23 (67.6)			
Calcification						
Yes	2 (7.7)	0 (0.0)	2 (5.9)		0.654[F]	1.000
No	24 (92.3)	8 (100.0)	32 (94.1)			
Fibrotic changes						
Yes	17 (65.4)	6 (75.0)	23 (67.6)	0.630 (0.105–3.781)	0.258[F]	1.000
No	9 (34.6)	2 (25.0)	11 (32.4)			
Tree-in -bud						
Yes	1 (3.8)	1 (12.5)	2 (5.9)	0.280 (0.015–5.067)	0.828[F]	0.421
No	25 (96.2)	7 (87.5)	32 (94.1)			
Nodes						
Yes	4 (15.4)	0 (0.0)	4 (11.8)		1.395[F]	0.551
No	22 (84.6)	8 (100.0)	30 (88.2)			
Pleural effusion						
Yes						
No	26 (100.0)	8 (100.0)	34 (100.0)			
Bilateral disease						
Yes	19 (73.1)	5 (62.5)	24 (70.6)	1.629 (0.306–8.679)	0.330[F]	0.666
No	7 (26.9)	3 (37.5)	10 (29.4)			
CT inactive disease						
Yes	18 (69.2)	6 (75.0)	24 (70.6)	0.750 (0.123–4.556)	0.098[F]	1.000
No	8 (30.8)	2 (25.0)	10 (29.4)			
CT active disease						
Yes	2 (7.7)	1 (12.5)	3 (8.8)	0.583 (0.046–7.425)	0.176[F]	1.000
No	24 (92.3)	7 (87.5)	31 (91.2)			

*χ2, Chi square test; OR, Odds ratio; 95% CI, 95% Confidence Interval; *p-value < 0.05; CT, Computed Tomography; F, ANOVA (Analysis of Variance)*

that target the organism rather than inflammation may help differentiate sterile infection post-treatment from latent bacteria.

Several non-FDG PET tracers have been investigated for imaging of tuberculosis to target different aspects of the pathophysiology of mycobacteria tuberculosis, such as 11 C-choline, (^{18}F)fluoroethylcholine (^{18}F-FEC), 30-deoxy-30-(^{18}F)fluoro-L-thymidine (^{18}F-FLT), 68Ga-citrate, (^{18}F) sodium fluoride (^{18}FNaF) and radiolabelled anti-TB drugs [26]. More specifically, PET radiolabelled anti-tuberculosis agents that bind to the organism have been used, such as (^{11}C) C-rifampicin, (11 C) isoniazid (INH), (^{18}F)F-linezolid and Bromine-76 bedaqualine ([^{76}Br]Br-bedaqualine) with some potentially promising results reported, however, their clinical application has not been comprehensively investigated [27].

Conclusion

The incidence of residual metabolic activity and complete metabolic response on end-of-treatment [^{18}F]F-FDG-PET/CT is similar between HIV-infected and uninfected patients. The incidence of [^{18}F]FDG-avid mediastinal/hilar lymphadenopathy is more prevalent among HIV-positive patients. The pattern of lung findings was not otherwise significantly different between HIV-positive and HIV-negative patients, indicating that the presence of HIV coinfection may not influence the interpretation of end-of-treatment [^{18}F]F-FDG-PET/CT obtained for pulmonary tuberculosis treatment response assessment. Among HIV-infected patients, suboptimal disease control by anti-retroviral therapy increases the risk of residual metabolic activity at the completion of anti-tuberculous therapy.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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