Original article

Clinical spectrum, risk factors and outcome of immune reconstitution inflammatory syndrome in patients with tuberculosis–HIV coinfection

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Background: Here, we aimed to determine the clinical spectrum, predictors and outcomes of paradoxical tuberculosis-immune reconstitution inflammatory syndrome (TB-IRIS) in a resource-limited setting.

Methods: In a prospective cohort, we studied 254 patients with tuberculosis and HIV coinfection commencing antiretroviral therapy (ART). We identified patients with TB-IRIS using the International Network for Studies Against HIV-Associated IRIS (INSHI) case definition. Risk factors and clinical outcomes of TB-IRIS were determined and reported.

Results: A total of 53 (21%) patients developed TB-IRIS a median of 2 weeks (IQR 12–22 days) after starting ART. The majority of the patients (70%) with TB-IRIS had extrapulmonary manifestations of TB-IRIS. In a multiple logistic regression model, baseline haemoglobin <100 g/l (OR 2.23 [95% CI 1.08–4.60]; P=0.031) and baseline CD4+ T-cell count <50 cells/µl (OR 4.13 [95% CI 1.80–9.51]; P=0.001) were significant predictors of IRIS. Seven additional patients fulfilled all INSHI criteria of TB-IRIS but had the episode of TB-IRIS later than 3 months after ART start.

Conclusions: TB-IRIS was a frequent reason for clinical deterioration among patients with TB commencing ART but was not a primary contributor to mortality. Patients with advanced CD4 depletion and anaemia were at increased risk of TB-IRIS. Some patients developed late-onset TB-IRIS and/or a recurrent TB-IRIS episode.

Introduction

The convergence of the tuberculosis–HIV (TB–HIV) pandemic is a major public health problem in resource-limited settings, accounting for one-third of the increase in cases of TB [1]. Combined antiretroviral therapy (ART) is beneficial in reducing morbidity and mortality due to TB–HIV coinfection [2,3]. However clinical management is challenged by drug–drug interactions, treatment toxicities, failure to adhere to treatment, drug-resistant TB and the TB immune reconstitution inflammatory syndrome (TB-IRIS). A better understanding of TB-IRIS is urgently required given that the

presentation of TB-IRIS as paradoxical clinical deterioration may be confused with drug toxicity, treatment failure or occurrence of a new opportunistic infection.

The pathogenesis of TB-IRIS is not clearly understood. It occurs as a result of dysregulated immunity when patients with advanced TB–HIV infection commence ART [4,5]. It is characterized by an exaggerated immunopathological response, presumably mediated by antigen-specific CD4 effector T-cells against live or dead TB organisms [6,7]. There is a strong increase in the number of tuberculin-specific cells among patients who develop

TB-IRIS, compared with those without the syndrome [8,9]. The following risk factors have been reported previously: low CD4^{+} T-cell count [10–12], extrapulmonary TB [13] and rapid viral suppression [14,15] after ART commencement. However, these risk factors were not consistently identified in all studies [16].

Most studies have been limited by small sample size, their retrospective nature and the lack of a common and validated case definition for TB-IRIS. The International Network of Studies Against HIV-Associated Immune Reconstitution Inflammatory Syndrome (INSHI) developed a consensus definition based on clinical criteria [17]. In this paper, we report the incidence and clinical predictors of TB-IRIS in a Ugandan cohort using the INSHI definition and describe the clinical spectrum and clinical outcomes of TB-IRIS. Risk factors for mortality in this cohort have been published previously [18].

Methods

Patient enrolment and baseline evaluation

Between 17 December 2007 and 31 December 2009, we screened patients for study eligibility and included participants who were ≥18 years of age, HIV-seropositive with a positive TB diagnosis as defined by microbiology or by the WHO criteria [19] and were eligible for ART initiation according to the Ugandan national ART treatment guidelines (CD4^{+} T-cell counts ≤250 cells/μl) [20]. Consenting patients willing to return for study visits and living within a 20 km radius were enrolled. We excluded patients with alanine transaminase or aspartate transaminases greater than 5× the upper normal limit and a serum creatinine >1.5 g/dl with clinical evidence of renal disease. Patients underwent a physical examination and investigations to confirm TB (sputum acid fast bacilli [AFB] stain and cultures on Lowenstein–Jensen media; lymph node aspirate stained for AFB; and pleural or ascitic fluid for cytology, AFB isolation and culture for TB). A chest X-ray, an abdominal ultrasound, a serum cryptococcal antigen (CrAG), hepatitis B surface antigen, C-reactive protein (CRP) and tuberculin skin test (TST; Tuberculin PPD RT 23 SSI; Statens Serum Institut, Copenhagen, Denmark) were performed at enrolment. A TST was considered positive when a skin induration of diameter >5 mm appeared at the TST placement site within 48–72 h of administration. A TST was repeated at months 2 and 6 following ART initiation, if the baseline or month 2 TST results were negative, respectively.

Treatment for newly diagnosed TB consisted of a standard fixed-dose induction combination chemotherapy for 2 months with isoniazid (H), ethambutol (E), rifampicin (R) and pyrazinamide (Z) followed by either rifampicin and isoniazid for the next 4 months (2EHRZ/4RH) or a combination of ethambutol and isoniazid for the next 6 months (2EHRZ/6EH). The first-line ART regimen was stavudine or zidovudine plus lamivudine with efavirenz or nevirapine.

Follow-up study visits and clinical care

Patients had study visits at baseline (ART start), 2 weeks, 1 month, 2 months, 3 months after commencement of ART and quarterly thereafter. Patients were instructed to return for assessment if they developed any worsening or new symptoms or signs suggestive of TB-IRIS. All patients had CD4^{+} T-cell counts repeated at months 6 and 12. TB monitoring was done according to National TB and Leprosy Programme (NTLP) guidelines (sputum AFB smears at month 2, 5 and treatment completion).

TB-IRIS work-up

A study medical officer assessed patients who developed worsening signs or symptoms following initiation of ART for TB-IRIS using the INSHI criteria. This included a symptom questionnaire, detailed physical examination and investigations to confirm the diagnosis of TB-IRIS or to exclude alternative causes. A repeat chest X-ray and abdominal ultrasound scan was done and compared with the baseline examination. Investigations were done to confirm presence of *Mycobacterium tuberculosis* or to exclude alternative infections. Mycobacterium isolates grown were tested for sensitivity to first-line TB drugs. CD4^{+} T-cell count and CRP were repeated at the time of TB-IRIS and plasma HIV RNA was measured retrospectively on stored baseline samples. A final diagnosis of TB-IRIS was made by consensus of two clinician investigators (WW and RC) using the INSHI definition [17] after review of all available investigations. We defined as 'late-onset TB-IRIS' patients who fulfilled all other INSHI criteria of TB-IRIS but in whom TB-IRIS occurred more than 3 months after ART start.

Ethical approval

The study was approved by the Makerere University College of Health Sciences Ethics committee, Mulago Hospital Research committee (Kampala, Uganda), the committee of Medical Ethics from the University of Antwerp and the Institute of Tropical Medicine (Antwerp, Belgium), and the Uganda National Council of Science and Technology. All participants provided written informed consent.

Statistical analyses

Baseline variables including age, sex, body mass index, CD4^{+} T-cell counts and haemoglobin, serum CRP, TB category (pulmonary/extrapulmonary), TST status and time from TB diagnosis to initiation of ART were evaluated as possible predictors of TB-IRIS using single

predictor and multiple logistic regression analysis. Variables with *P*-values <0.2 in the single predictor logistic regression models were included in the multiple logistic regression model, which was simplified using stepwise deletion. For this analysis, we used pairwise deletion for variables with up to 5% of values missing (TST status, 10/254 values missing) and the missing indicator method for variables with >5% of values missing (serum CRP, 64/254 values missing).

Results

Of 376 participants coinfected with HIV–TB and eligible for the study, 302 were enrolled and 254 started TB treatment and ART (Figure 1). The median age of patients enrolled was 34.5 years (SD 8.3) and 112 (44%) were female. Most patients had pulmonary TB (PTB) 196 (77%), 44 (17%) had extrapulmonary TB (EPTB) and 14 (6%) had both PTB and EPTB. Their median CD4$^+$ T-cell count was 52 cells/µl (IQR 19–128) and the median duration from the start of TB treatment to ART initiation was 44 days (IQR 28–64).

A total of 234 (92%) patients had at least 3 months follow-up from ART initiation. There were 20 (8%) patients who started ART but did not complete 3 months for the following reasons: 16 (80%) patients died, 2 (10%) transferred out, 1 (5%) patient withdrew consent and 1 (5%) was lost to follow-up. Of the 16 patients who died, the cause of death was due to Kaposi's sarcoma (*n*=2), Kaposi's sarcoma-immune reconstitution (*n*=1), gastroenteritis with severe dehydration (*n*=3), severe anaemia (*n*=2), liver failure (*n*=1), renal failure (*n*=1), sepsis (*n*=1), pulmonary embolism (*n*=1), pneumonia (*n*=1), progressive TB disease (*n*=1) and unknown causes (*n*=2).

TB-IRIS diagnoses

A total of 77 study participants who experienced worsening clinical symptoms while on ART were evaluated for TB-IRIS. After a complete clinical record review by WW and RC, 17 (22%) patients evaluated were considered not to have TB-IRIS for the following reasons: in 7, only 1 minor INSHI criterion was documented, 2 had poor adherence to ART and TB treatment and worsening of symptoms was attributed to untreated TB disease; in 8 patients an alternative diagnosis was likely (1 patient had culture-proven pulmonary pneumococcus infection, 1 patient had malaria [patient improved during anti-malarial treatment], 2 patients had another opportunistic disease as TB diagnosis was not confirmed microbiologically at baseline and both had poor response to TB treatment, 1 patient had ART treatment failure and 3 patients had two minor criteria for TB-IRIS that were transient). We identified 53 patients as having

Figure 1. Flow diagram for patients with TB–HIV coinfection enrolled into the TB-IRIS study
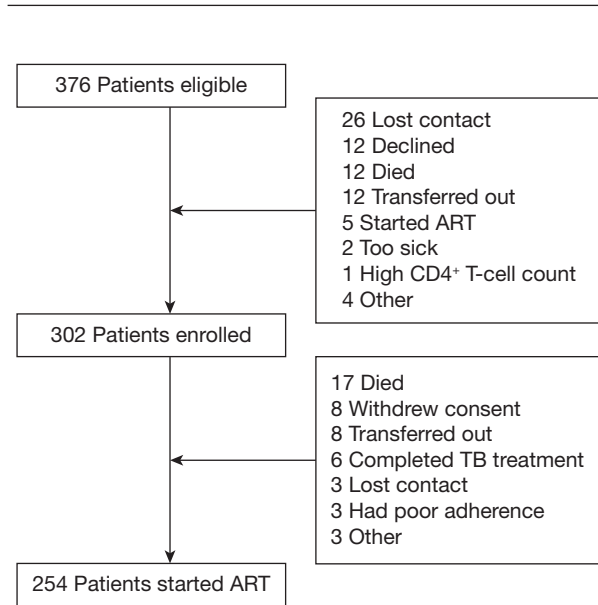
ART, antiretroviral therapy; TB, tuberculosis; TB-IRIS, tuberculosis immune reconstitution inflammatory syndrome.

TB-IRIS according to the INSHI case definition. This represents 21% of patients who started ART. Median time from ART start to TB-IRIS was 14 days (IQR 12–22; Figure 2). In addition, we diagnosed 7 (3%) patients with late-onset TB-IRIS a median 196 days (IQR 123–256) after ART start.

New or increasing lymphadenopathy (53%) was the most common major INSHI criterion among TB-IRIS cases (Table 1). 40 (75%) patients diagnosed with TB-IRIS had at least one major clinical criterion and 41 (77%) had at least two minor criteria for the diagnosis of TB-IRIS according to INSHI definition. 13 (25%) patients were classified as TB-IRIS based on minor criteria only (8 had two minor criteria and 5 had three minor criteria).
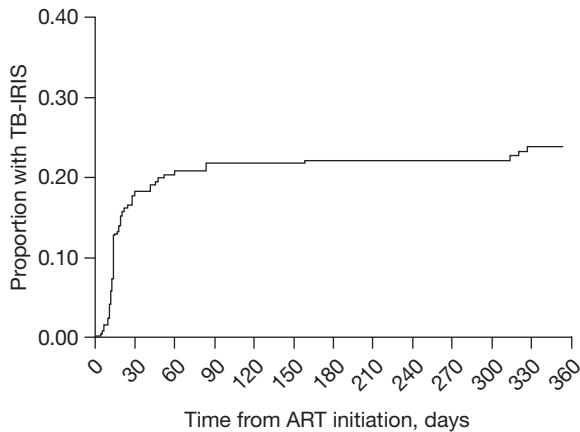
Clinical manifestations of TB-IRIS

The majority (37/53 [70%]) of the clinical presentations of TB-IRIS were extrapulmonary and 13/53(25%) were pulmonary. There were 10 (19%) patients who had both pulmonary and extrapulmonary manifestations. There were 13 patients in whom TB-IRIS was diagnosed based on only minor INSHI criteria and who did not fit in either category. Among the 37 patients diagnosed with extrapulmonary TB-IRIS, 24 (65%) had a baseline diagnosis of PTB alone at the start of ART.

Patients with late-onset TB-IRIS had clinical signs and symptoms similar to those who were diagnosed earlier (Table 2; Additional file 2) and 6 (86%) had

extrapulmonary manifestations of TB-IRIS. A higher proportion of patients with a negative TST at baseline converted to positive among the patients who developed TB-IRIS in the first 3 months (21/53 [40%]) compared with those with late-onset TB-IRIS (2/7 [29%]),

but this was not statistically significant. The proportion of TST converters among TB-IRIS patients was also greater than proportion among 49/249 (20%) patients who did not develop TB-IRIS.

Four patients had a recurrent episode of TB-IRIS. In two patients the first episode of TB-IRIS happened within the first 3 months of ART and in all four patients the recurrence of TB-IRIS happened after 3 months of ART (4, 8, 18 and 21 months after ART start). TB-IRIS recurrence was in the same anatomic location in two patients (recurrence of ankle swelling with abscess formation and ulceration, and a supraclavicular abscess in the location of a previously enlarged cervical lymph node) and in a different location for the other two patients (one initially presented with ascites and at recurrence had a supraclavicular abscess, the second had increased cervical adenopathy at the first episode and multiple abscesses at recurrence).

Predictors of TB-IRIS

Baseline CD4+ T-cell counts <50 cells/μl, a baseline haemoglobin <100 g/l, a negative baseline TST result and a diagnosis of extrapulmonary disease at baseline were univariately associated with an increased risk of TB-IRIS (Table 3). In a multiple logistic regression model, haemoglobin <100 g/l and CD4 lymphocyte count <50 cells/μl remained independently significant baseline predictors for development of TB-IRIS.

Treatment and outcomes of patients who developed TB-IRIS

Twelve (23%) patients with TB-IRIS were hospitalized. Of the 41 patients who were not hospitalized, 20 (49%) needed one, 3 (7%) needed two and 5 (12%) needed at least three additional TB-IRIS-related clinic visits. The remaining 13 (32%) did not need further treatment. One patient was lost to follow-up. Of the remaining 52 patients, 47 (90%) fully recovered following the TB-IRIS episode. Five (10%) patients who had been diagnosed with TB-IRIS died and in 4 (80%) of these an alternative contributing cause of death such as lobar pneumonia (*n*=1), intestinal obstruction (*n*=1), advanced TB infection (*n*=1) and respiratory failure secondary to aspiration (*n*=1) was identified. In one patient the cause of death was not determined.

Discussion

Using the standardized INSHI definition, we diagnosed TB-IRIS in one-fifth of ART-naive patients coinfected with TB–HIV within 3 months of starting ART. This is a higher proportion of TB-IRIS than has been previously reported from resource-limited countries with a high TB and HIV burden [14,21,22]. This difference, however, may be related to the use of different TB-IRIS

Figure 2. Kaplan–Meier curve showing the cumulative occurrence of TB-IRIS with time

ART, antiretroviral therapy; TB-IRIS, tuberculosis immune reconstitution inflammatory syndrome.

Table 1. Frequency of clinical characteristics among patients with TB-IRIS

Criteria	Frequency, *n* (%)[a]
Major criteria	
Increasing lymphadenopathy	28 (53)
Worsening abdominal ultrasound findings	16 (30)
Worsening chest X-ray features	13 (25)
Abscesses	3 (6)
Other focal tissue swelling	2 (4)
Tuberculous meningitis	0 (0)
Tuberculous ascites	3 (6)
Tuberculous pericarditis	1 (2)
Tuberculous pleural effusion	0 (0)
Joint effusion	0 (0)
Minor criteria	
Fever	45 (85)
Weight loss	30 (57)
Night sweats	26 (49)
Cough	36 (68)
Dyspnea	29 (55)
Stridor	1 (2)
Peritonitis	9 (17)
Abdominal pain and lymphadenopathy	8 (15)
Abdominal pain and hepatomegaly	6 (11)
Abdominal pain and splenomegaly	3 (6)

[a]*n*=53. TB-IRIS, tuberculosis immune reconstitution inflammatory syndrome.

Table 2. Characteristics of patients with late-onset TB-IRIS

Age, years	Sex	CD4 lymphocyte count, cells/µl			TB category	TST	TST conversion	Time from ART start to IRIS, days	Manifestation of TB-IRIS	Number of INSHI criteria	
		ART start	TB-IRIS	Month 6						Major	Minor
40	Male	52	48	194	PTB	Negative	Converted	118	EPTB-IRIS	2	2
44	Male	5	95	52	PTB	Negative	Not converted	243	EPTB-IRIS	1	1
45	Female	21	222	65	PTB	Negative	Not converted	307	PTB and EPTB-IRIS	2	3
35	Male	80	121	150	PTB	Negative	Converted	196	EPTB-IRIS	2	1
51	Female	211	175	322	PTB	Negative	Not converted	145	PTB-IRIS	1	2
36	Male	27	175	114	PTB	Negative	Not converted	256	EPTB-IRIS	1	0
30	Female	64	257	250	PTB	Negative	Not converted	123	EPTB-IRIS	1	0

ART, antiretroviral therapy; EPTB, extrapulmonary tuberculosis; EPTB-IRIS, extrapulmonary manifestation of TB-IRIS; INSHI, International Network for Studies Against HIV-Associated Immune Reconstitution Inflammatory Syndrome; PTB, pulmonary tuberculosis; PTB-IRIS, pulmonary manifestation of TB-IRIS; TB, tuberculosis; TB-IRIS, tuberculosis immune reconstitution inflammatory syndrome; TST, tuberculin skin test.

Table 3. Baseline predictors of TB-IRIS in 254 TB–HIV-coinfected patients starting antiretroviral therapy: univariate and multiple logistic regression

Characteristic	Univariate		Multivariate	
	OR (95% CI)	*P*-value	Adjusted OR (95% CI)[a]	*P*-value
Age				
≥35 years	0.72 (0.38–1.34)	0.299	–	–
<35 years	1		–	–
Gender				
Male	0.96 (0.52–1.78)	0.908	–	–
Female	1		–	–
BMI[b]				
<18.5 kg/m²	0.85 (0.46–1.56)	0.595	–	–
≥18.5 kg/m²	1		–	–
Haemoglobin				
<100 g/l	**2.35 (1.17–4.75)**	**0.017**	**2.23 (1.08–4.60)**	**0.031**
≥100 g/l	1		1	
CD4+ T-cell counts				
<50 cells/µl	**4.24 (1.87–9.66)**	**0.001**	**4.13 (1.80–9.51)**	**0.001**
50–100 cells/µl	1.32 (0.43–4.07)	0.627	1.32 (0.42–4.09)	0.636
>100 cells/µl	1		1	
C-reactive protein				
Unknown[c]	1.48 (0.59–3.71)	0.401	–	–
≥5 mg/l	1.10 (0.48–2.53)	0.820	–	–
<5 mg/l	1		–	–
TB category				
Extrapulmonary TB	**2.07 (1.06–4.03)**	**0.032**	–	–
Pulmonary TB	1		–	–
Tuberculin skin test reaction[d]				
Negative	**2.50 (1.15–5.45)**	**0.021**	–	–
Positive	1		–	–
Time from TB treatment to ART start				
<30 days	2.00 (0.89–4.46)	0.092	–	–
30–60 days	1.01 (0.46–2.22)	0.979	–	–
>60 days	1		–	–

[a]From a multiple logistic regression model with only independently significant predictors. [b]One participant did not have baseline body mass index (BMI) due to missing weight data. [c]64 participants did not have baseline C-reactive protein results. [d]10 participants did not have baseline tuberculin skin test results. Statistically significant values are in bold. ART, antiretroviral therapy; BMI, body mass index; TB, tuberculosis; TB-IRIS, tuberculosis immune reconstitution inflammatory syndrome.

case definitions. The prospective nature of our study in which patients were evaluated against the INSHI case definition and availability of all clinical information led to a more complete estimate compared with retrospective studies. Patients developed TB-IRIS a median of 2 weeks after starting ART, which is consistent with findings from most previous retrospective and prospective studies [22–25]. The median duration from the start of TB treatment to the start of ART was 44 days (IQR 28–64). Most studies report that a shorter period from TB treatment to ART is associated with an increased risk of TB-IRIS [15,21,24,26–28]. Our study and a few other studies, however, do not demonstrate this [22,29]. This may be due to the wide variability in the time from TB treatment start to ART initiation. Only 71 (28%) patients started ART <30 days after TB treatment start. Two recent randomized trials investigating the optimal time for ART initiation [3,27], the AIDS Clinical Trials Group (ACTG) 5221 and the Starting Antiretroviral Therapy at 3 Points in Tuberculosis (SAPiT) trial, found that immediate initiation of ART in patients with CD4+ T-cell count <50 cells/μl prevented mortality and progression to new AIDS-defining illness or death [28,30]. Similar benefit was reported by the CAMbodia Early versus Late Initiation of ART (CAMELIA) trial, which demonstrated an improved survival benefit of ART initiation within 2 weeks of TB treatment compared with 8 weeks [3]. Data collection for our study was concluded much before the above mentioned studies that demonstrated a potential for increased incidence of paradoxical TB-IRIS with a shorter TB lead-in period.

Extrapulmonary disease manifested in 70% of the patients diagnosed with TB-IRIS. EPTB is considered an advanced form of TB disease and has been associated with increased risk of TB-IRIS [31]. In this cohort, despite the low CD4+ T-cell counts, most of the patients were diagnosed with PTB. This is possibly due to referral bias as most patients referred to this clinic fulfill the National TB programme recommendation that emphasizes treatment of smear positive PTB (146 [74%] PTB patients had smear positive disease). These guidelines have recently been revised to incorporate recommendations by the WHO on treatment of smear negative PTB disease and EPTB [32]. 65% of patients who presented with extrapulmonary manifestations of TB-IRIS had a baseline diagnosis of PTB. This indicates that most patients with HIV and low CD4+ T-cell counts who are diagnosed with PTB have, in fact, disseminated disease and may later present with features of TB-IRIS at extrapulmonary sites after ART initiation. Most manifestations of extrapulmonary TB-IRIS were peripheral (76%) or abdominal (43%) lymphadenopathy. This predominantly extrapulmonary presentation of TB-IRIS has also been observed in other studies [22,23,33]. Monitoring for new or worsening manifestations of

extrapulmonary disease among populations at risk may be useful to identify patients with TB-IRIS early.

CD4+ T-cell counts <50 cells/μl were independently associated with increased occurrence of TB-IRIS. Most studies have reported this association of advanced CD4 lymphocyte count depletion with TB-IRIS [10,11,21,29,33]. In this cohort the median CD4+ T-cell count was 52 cells/μl and this was associated with a high incidence of TB-IRIS despite a 6-week delay in the initiation of ART following TB treatment. In addition, anaemia (haemoglobin <100 g/l) was associated with a twofold increase in the risk of TB-IRIS. Anaemia may result from chronic HIV infection and nutritional deficiency, but may also be a reflection of disseminated TB disease affecting the bone marrow.

Most patients in this study presented with mild to moderate forms of TB-IRIS and were treated with nonsteroidal anti-inflammatory drugs and other analgesics, aspiration of abscesses and a small proportion (8%) received steroids. At the time of the study, there was little evidence regarding the benefits of specific modes of therapy. A recent randomized trial by Meintjes *et al.* [34] showed the benefit of steroids in reducing hospitalization and the need for therapeutic procedures in patients with TB-IRIS but there was no difference in overall mortality. 90% of our patients recovered fully following the TB-IRIS episode. Mortality occurred in 10% of TB-IRIS patients and was associated with identifiable comorbid illnesses in most cases. TB-IRIS was therefore not a primary contributor to mortality in these patients. Other cohorts have also shown that TB-IRIS, with the exception of IRIS caused by a central nervous system TB infection [35], is not a major cause of mortality among patients commencing ART [10,13,22,36]. None of our patients had central nervous system TB.

The baseline characteristics and clinical features of patients with late-onset TB-IRIS (which occurred in 3% of the patients in this study) were similar to those of patients fulfilling strict INSHI criteria (Additional file 2). The incidence of late-onset TB-IRIS and the rate of TB-specific immune recovery while on ART need to be determined in prospective long-term follow-up studies. Huyst *et al.* [37] reported a case of late-onset TB-IRIS, which presented 4 years after starting ART, and other forms of IRIS frequently occurring after 3 months of ART include cryptococcal-immune reconstitution [38].

Our study was carried out under programmatic circumstances. An important limitation of the study was the high loss to follow-up prior to ART commencement. Of the patients enrolled in the study and eligible for ART, 16% did not commence ART. Study participants who did not start ART had a higher median CD4+ T-cell count compared with those who started ART, but this was not statistically significant (Additional file 3).

A higher median CD4$^+$ T-cell count would lead to fewer cases of TB-IRIS in the cohort. The group that did not start ART also had a higher CRP level, which was statistically significant. CRP is acute phase protein that is raised in systemic inflammation. This might indicate that the patients who did not start ART had a stronger immunity, had additional comorbid illnesses or had more disseminated TB disease.

In conclusion, TB-IRIS is a common reason for clinical deterioration among patients with TB commencing ART but in itself is not associated with increased mortality. Advanced immunodeficiency with CD4$^+$ T-cell counts <50 cell/µl and anaemia are each independent predictors of IRIS. TB-IRIS predominantly manifested as extrapulmonary disease, even in patients diagnosed with pulmonary TB at the start of ART, suggesting that in patients with low CD4$^+$ T-cell count TB is generally a disseminated disease. Other forms of TB-IRIS including late-onset and recurrence of TB-IRIS do also occur but in a minority of patients.

Acknowledgements

Disclosure statement

The authors declare no competing interests.

Additional files

Additional file 1: A list of the members of the TB-IRIS study group can be found at http://www.intmedpress.com/uploads/documents/AVT-11-OA-2255_Worodria_Add_file1.pdf

Additional file 2: A comparison of baseline characteristics of patients with late-onset TB-IRIS versus TB-IRIS according to the INSHI case definition can be found at http://www.intmedpress.com/uploads/documents/AVT-11-OA-2255_Worodria_Add_file2.pdf

Additional file 3: A comparison of baseline characteristics of patients with TB–HIV by antiretroviral status can be found at http://www.intmedpress.com/uploads/documents/AVT-11-OA-2255_Worodria_Add_file3.pdf

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