

**ORIGINAL ARTICLE****TB–HIV co-infection: a catastrophic comradeship**

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The symbiotic association of tuberculosis (TB) and HIV poses a challenge to human survival. HIV complicates every aspect of TB including presentation, diagnosis and treatment. HIV–TB patients encounter unique problems like drug–drug interactions, cumulative toxicity, immune reconstitution inflammatory syndrome (IRIS), lower plasma drug levels and emergence of drug resistance during treatment despite adherence. TB may also be overdiagnosed in HIV due to a number of diseases that closely resemble TB. Notable among them are non-tuberculous mycobacteria, *Pneumocystis jirovecii* and *Nocardia*. Even though diagnostic procedures have improved over the years, patients in developing countries usually seek health care at later stage of the disease. Research data ascertains the duration of therapy for TB to be 6 months with rifampicin and isoniazid, reinforced with ethambutol and pyrazinamide in the first 2 months. The schedule of therapy is still debatable with daily regimens being preferred in the context of HIV. Many reasons exist for persistence of *Mycobacterium Tuberculosis* (M.TB) in sputum, or delayed-clearance of TB from sputum smears in HIV, apart from emergence of drug resistance and non-compliance. Acquired rifampicin resistance (ARR) is a unique phenomenon complicating HIV-associated TB when an intermittent regimen of antituberculosis therapy (ATT) is used without timely initiation of highly active antiretroviral therapy (HAART), especially in patients harbouring isoniazid-resistant strains. Immune restoration is often incomplete ('swiss cheese' pattern) even with effective HAART if not started early. Immune reconstitution inflammatory syndrome (IRIS) is the paradoxical worsening of the patient's condition often with radiological deterioration, due to an enhanced immune response with HAART. IRIS occurs despite an effective virological suppression and a favourable response to ATT. The incidence of IRIS in HIV has

reached up to 54%, requiring utilization of experts and tertiary care which forms an obstacle to the decentralization of patients in the ART programme. Research in HIV–TB immunology and management needs further exploration in order to understand the diseases and offer appropriate treatment. The following paragraphs provide scientific evidences generated through research that could potentially guide management.

Oral Diseases (2016) 22, 46–52**Keywords:** HIV; TB; IRIS; ATT; ART; HAART**Introduction**

Tuberculosis is the most common opportunistic infection and the most common cause of pyrexia of unknown origin occurring in HIV in India (Kejariwal *et al*, 2001). The perfect symbiosis maintained between the retrovirus and the mycobacterium has mutually helped both the epidemics in their rapid spread across the globe. The latest WHO global tuberculosis report 2014 reveals that there were 1.2 million co-infected individuals in India at the end of 2013 and the mortality due to TB–HIV is significant, amounting to 38 000 cases (WHO, 2014a,b). There is a need for physicians dealing with these cases to be aware of the complex interactions between both the diseases so that the balance maintained by the two pathogens can be tilted to our advantage in our attempt to maximize response to therapy (Figure 1).

Diagnostic issues in HIV-TB

There has been a paradigm shift in diagnostic approaches towards TB in HIV. Even though pulmonary TB is the most common type of TB among HIV-infected patients, the yield of sputum smear positivity is comparatively low. HIV masks the classical symptoms and signs of TB leading to atypical pattern in chest X-rays and in computed tomography. Clearly marginated cavities and haemoptysis are conspicuous by their absence. This leads to delays in seeking health care and also late recognition of this opportunistic infection. As HIV predisposes to other infections

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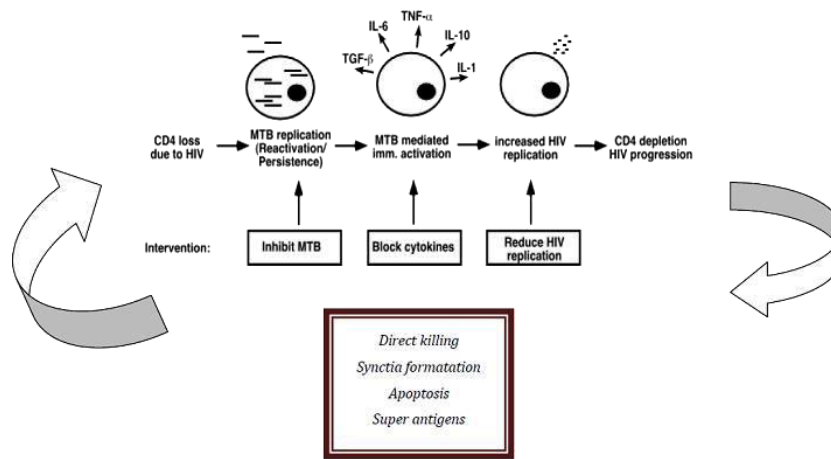


Figure 1 The immunological symbiosis between Mycobacterium Tuberculosis and HIV

apart from TB, every effort must be undertaken to confirm TB, when clinically suspected, especially in advanced AIDS. The introduction of Xpert-MTB Rif has revolutionized TB diagnosis, yielding quicker results, with a sensitivity from 70% to 90% among HIV patients with smear-positive TB vs 43% to 61% sensitivity in HIV patients with smear-negative TB (Lawn *et al*, 2011). Emphasis should be laid on collection of good quality sputum which should be mucoid or mucopurulent with a volume of at least 2–3 ml. Admixture of blood or saliva in sputum lowers the yield. Evaluation of three sputa specimens increases the sensitivity to 90%. Test for rifampicin resistance using Xpert-MTB Rif has sensitivity above 95%. Evaluation of tools for improving diagnosis in extra-pulmonary TB is an important upcoming research field (Lawn *et al*, 2011; Scott *et al*, 2014). The yield of *M. Tuberculosis* from other extra-pulmonary specimens is provided in Table 1.

Antituberculosis therapy in HIV co-infected

The duration and schedule of TB therapy in HIV have been recognized as key research issues in India. For a long time, it was stressed that a longer duration of TB therapy was essential in HIV–TB. The study by Swaminathan *et al* (2010) that compared a 6-month intermittent therapy of ATT against a 9-month therapy (with an extended continuation phase of 3 months) found the treatment outcomes at the end of therapy to be equivocal, with similar incidence of overall recurrences. The

meta-analysis by Menzies *et al* (2009) demonstrated that additional treatment beyond 6 months (up to 8 months) did not increase the efficacy further, justifying the current duration of 6 months. Currently, the global WHO recommendation is to use a 6-month regimen of INH, rifampicin, ethambutol and pyrazinamide, with daily dosing at least in the intensive phase followed by INH and rifampicin given daily or thrice weekly (Standards of TB Care in India, 2014).

Narendran *et al* (2014) in the cross-protocol analyses comparing three cohorts – TB without HIV, TB with HIV infection in the pre-HAART era and HIV–TB with ART – found that pretreatment INH resistance and HIV infection at baseline were significantly associated with the emergence of rifampicin resistance, when an intermittent regimen of ATT is used with concomitant HAART.

A recent systematic review by Faiz Khan highlighted salient findings with regard to the schedule of TB therapy. Intermittent therapy in the intensive phase was associated with more failures [adjusted relative risk, 4.0; 95% confidence interval (CI), 1.5–10.4] and relapses [adjusted relative risk, 4.8; 95% CI, 1.8–12.8] compared to daily ATT therapy. In HIV–TB patients, extended rifampicin duration (up to 6 months), daily dosing and use of ART improved TB treatment outcomes. The benefits of extended rifampicin duration and daily dosing, however, were unclear in the presence of ART (Ahmad Khan *et al*, 2012).

A change in the regimen from intermittent to daily, however, lacks trial data till date. Increased/additive drug toxicity and the feasibility of DOTS, when a daily ATT regimen is used in the programme, are other challenges. The National Institute for Research in Tuberculosis (NIRT) is currently conducting a randomized controlled clinical trial comparing daily vs intermittent therapy of ATT in HIV, dealing with important issues in co-infection such as efficacy, emergence of drug resistance, toxicity, drug levels and immune reconstitution inflammatory syndrome (IRIS) (Narendran, 2009). The study would also determine whether it is only a subset of advanced HIV who may be benefitted or by daily dosing or it is required by all HIV-infected TB patients irrespective of the stage of immunodeficiency.

Table 1 Sensitivity and specificity of Xpert-MTB Rif in extra-pulmonary specimens (Scott *et al*, 2014)

Type of specimen	Sensitivity %	CI%
Pus	91	76–94
Lymph nodes	80	56–94
Cerebrospinal fluid	81	59–92
Ascitic fluid	59	44–58
Pleural fluid	44	

Overall sensitivity – 59% (53–65) and specificity – 92% (90–94%).

Non-responders to ATT (persistent positivity): NIRT experience

Alcoholism is a barrier to drug adherence. Addiction counselling for alcoholism, substance abuse and smoking needs to be integrated into the programme, especially for managing co-infection. Both TB and HIV, being chronic infections, demand a high adherence rate to avoid the emergence of drug resistance. When patients present with a persistently low CD4 either with a detectable viral load even after 6 months of ART (virological failure) or with advanced HIV with undetectable VL without a corresponding rise in CD4 count (immunological discordance), delayed smear conversion is inevitable and relapses are common. The closest in differential diagnosis of IRIS is drug-resistant TB (Narendran and Swaminathan, 2013). Usually, in paradoxical IRIS, the cultures are negative for *Mycobacterium tuberculosis*, unless IRIS occurs with a shorter ATT-ART interval (Narendran and Swaminathan, 2013). Malabsorption of drugs can lead to subtherapeutic levels, leading to delayed sputum conversion that manifests as persistence of fever. Increase in dosage of ATT with close monitoring of liver and renal function tests can help solve the problem. Research questions include optimal ATT drug dosage especially INH and rifampicin in dual infection weighing toxicity versus efficacy.

Various species of non-tuberculous mycobacteria can mimic TB in smear, but the corresponding cultures in the LJ medium could be negative. Some of the common species frequently identified in our part of the country are *M. kansasii*, *M. chelonae*, *M. abscessus* and *M. avium-M. intracellulare* especially in advanced HIV.

Some patients may become culture positive, especially when nearing end of their treatment period. The sputum culture may show a grade of a few colonies only, but which is resistant to many antituberculosis drugs, a phenomenon called 'bacillary escape' coined by Caminero (2006). Patients need to be counselled and cultures repeated. Usually, these patients are asymptomatic without evidence of clinical or radiological deterioration. Importantly, this condition does not require any modification of treatment.

Acquired rifamycin resistance – a phenomenon complicating HIV-associated TB

Acquired rifamycin resistance (ARR) is the emergence of resistance to rifamycin among patients whose initial isolates were sensitive at the start of ATT (defined as MIC < 128 µg ml⁻¹). This phenomenon of ARR is, however, rare in HIV-sero-negative individuals with TB. In a cohort of 1435 HIV-sero-negative patients with drug-susceptible TB enrolled in various trials at the Tuberculosis Research Centre (currently NIRT), Chennai, only four patients developed rifampicin resistance, irrespective of the dosing schedule (Tuberculosis Research Centre, 2001).

Acquired rifamycin resistance in HIV co-infected had been described with intermittent regimens using all rifamycins, namely rifapentine given once weekly (Vernon *et al*, 1999), rifabutin twice weekly (Nahid *et al*, 2007) and rifampicin thrice intermittently (Swaminathan *et al*, 2010). Advanced stage of HIV, absence of HAART,

extensive and/or disseminated TB, initial H-resistance and suboptimal drug concentrations due to malabsorption all of them play a role in ARR causation. Increased tissue bacillary load in HIV, coupled with defective clearance due to subdued immune apparatus, apparently leads to selection of genomic mutants resistant to rifampicin, which is more pronounced in the face of baseline INH resistance (Perlman *et al*, 2005; Swaminathan *et al*, 2010).

Newer anti-TB drugs in the pipeline

Bedaquiline (TMC 207) is one of the newer drugs conditionally approved by the FDA recently for use in the treatment of MDR-TB, especially when choices are limited. It is a diarylquinoline derivative that shows activity against ATP synthetase that takes 3–5 days for perception of its bactericidal effect, and has an extremely long half-life of 4–5 months. Drug–drug interactions occur with CYP3A4 inducers (e.g. rifampicin reduced bedaquiline exposure by approximately 50% obviating co-administration). The most important side effects are QTc prolongation, arthralgia, headache and vomiting (Centers for Disease Control and Prevention, 2013). Other drugs in the phase 2b and phase three stages include delamanid and PA-824. Newer derivatives of sutezolid, AZD 5487, radezolid and tedizolid which are devoid of the myelosuppressive side effects of the linezolid, their predecessor, are also in the pipeline (Zumla *et al*, 2014). Data on usage of these drugs in HIV–TB-co-infected group and in the drug-susceptible group are still limited.

Concurrent HAART therapy in HIV–TB

Improved TB outcomes in HIV emphasize the need for early ART initiation. The current WHO (WHO, 2014a,b) and the NACO (DHHS, 2014) guidelines recommend ART initiation irrespective of CD4 in HIV–TB infection within 2–8 weeks of ATT, after the patient stabilizes with ATT.

The most widely used combination of first-line ART in resource-limited settings includes three drugs: two nucleoside reverse transcriptase inhibitors (NRTIs) – either tenofovir or zidovudine along with lamivudine, and one non-nucleoside reverse transcriptase inhibitor preferably efavirenz (EFV) in the dosage of 600 mg (NNRTI) (WHO, 2014a,b). Efavirenz trough concentration is an important determinant of its virological activity. While efavirenz dose (600 mg vs 800 mg) and concurrent rifampicin administration have a lesser impact (Manosuthi *et al*, 2006), a polymorphism in the CYP2B6 gene (G to T mutation) results in significantly higher blood levels of the drug leading to increased risk of neuro-psychiatric toxicity (Ramachandran *et al*, 2009).

Use of nevirapine (available as generic fixed-drug combination) is not recommended routinely with rifampicin, unless there is a contraindication to efavirenz, like pregnancy (in India) or psychiatric illness. In the rare instance of using nevirapine, it should be introduced in the full dose of 200 mg BD preferably when the viral load is effectively undetectable, for maximizing benefits (Manosuthi *et al*, 2012). Triple NRTI regimens containing aba-

cavir can be used alternatively [in patients negative for HLA B57:0], but have been associated with inferior outcomes in patients with a higher viral load (Munderi *et al*, 2010). A quadruple NRTI regimen including tenofovir has been found to be as effective as EFV-based regimen in smaller trials (Moyle *et al*, 2006). All HIV-TB patients should receive high-dose pyridoxine (100 mg) and cotrimoxazole (one tablet double strength) prophylaxis along with ATT.

Timing of ART in HIV

Early initiation of HAART reduces mortality and morbidity due to HIV and TB, with faster sputum conversion (Nahid *et al*, 2007). The SAPIT (Havlir *et al*, 2011) and the ACTG 5221 (Abdool Karim *et al*, 2011) trials have clearly concluded that ART needs to be immediately initiated (within 2 weeks) only in patients with $CD4 < 50 \text{ cells mm}^{-3}$, while for patients with a $CD4 > 50 \text{ cells mm}^{-3}$, ART can be started between 2 weeks and 12 weeks without any compromise on survival benefits. This strategy is beneficial in reducing toxicity and IRIS at the same time.

Paradoxical IRIS – ‘The predestined fury of the perturbed immunity’

Tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS) is the paradoxical worsening of symptoms and signs of TB, despite a favourable immunological recovery, as evidenced by an effective reduction of HIV plasma viral load by at least $0.5 \log \text{ copies ml}^{-1}$ (Meintjes *et al*, 2008; Gopalan *et al*, 2014). The incidence can be as high as 54% (Narendran *et al*, 2013). TB-IRIS, the most common form of IRIS, is classified into two types: (1) paradoxical TB-IRIS that occurs in patients started on ATT and subsequently started on ART, and (2) unmasking TB-IRIS or antiretroviral therapy (ART)-associated TB that manifests in asymptomatic individuals who are started on ART, but without a prior diagnosis of TB, being either subclinical or undiagnosed earlier (Narendran and Swaminathan, 2013). Paradoxical IRIS is easier to diagnose, because of its biphasic pattern: an initial phase of improvement when ATT is started, followed by ‘paradoxical’ deterioration following ART initiation.

The most consistent risk factors are a very low CD4 cell count, low CD4/CD8 ratio, lower haemoglobin and weight, disseminated and extra-pulmonary TB disease, with the presence of other concomitant opportunistic infection at the time of ART initiation (Narendran *et al*, 2013; Gopalan *et al*, 2014). Shorter duration of pathogen-specific therapy at the time of starting ART has always remained a constant risk factor (Narendran *et al*, 2013). A study on paradoxical IRIS in a pure cohort of culture-positive rifampicin-sensitive pulmonary TB patients with HIV (ART naïve) subsequently started on ATT and HAART showed an IL-6 and CRP to be reliable predictors of IRIS (Narendran *et al*, 2013).

Pathogenesis of TB-IRIS

The current scientific data suggest that functional restoration of immune-competent cells (CD4) and their redistribu-

tion to the site of lesion unleashes an immune response, including a cytokine outburst, that results in IRIS. There is an overriding Th1 response, over Th2, with its associated inflammatory cytokines culminating in IRIS (Bourgarit *et al*, 2006). The majority of paradoxical IRIS cases occur within the first 3 months post-ART. (Gopalan *et al*, 2014). Contrary to the earlier belief that the T regulatory cells (Tregs) which are the committed suppressors of the immune system are partially restored, it has been recently found that the Treg numbers are normally restored post-ART, but are functionally defective, tilting the scale in favour of an inflammatory response (Seddiki *et al*, 2009).

Clinical features of TB-IRIS

Fever with rigour or chills (resembling malaria) and lymph node enlargement are the most common manifestations in TB-IRIS (Narendran and Swaminathan, 2013; Narendran *et al*, 2013). Symptoms vary in severity from localized superficial lymphadenopathy and subcutaneous abscesses to severe forms like adult respiratory distress syndrome, meningitis, space occupying lesions like tuberculomas and viscus perforation, which can end fatally. Compressive syndromes include stridor due to tracheal narrowing and superior vena caval (SVC) syndrome caused by upper mediastinal group of nodes enlargement (Buckingham *et al*, 2004). Patients with abdominal TB may present with pain and diarrhoea. Other abdominal manifestations include hepato-splenomegaly, psoas abscesses, splenic micro-abscesses, splenic rupture, viscus perforation, epididymo-orchitis, ureteric compression and acute renal failure (Lawn *et al*, 2008). Osetomyelitis, subcutaneous abscesses and thromboembolic episodes have also been reported (Breton *et al*, 2004). Radiological worsening in pulmonary TB without symptoms or ‘cryptic IRIS’ has been reported in a number of studies in NIRT in TB patients, even in the pre-HIV era (Narendran and Swaminathan, 2013).

TB-IRIS diagnosis

The only objective sign of IRIS is a reduction in viral load of at least $0.5 \log_{10}$ with or without increase in CD4 count after excluding toxicity, therapeutic failure and drug resistance (Meintjes *et al*, 2008; Gopalan *et al*, 2014). ART initiation, substitution or ART interruption followed by re-initiation can all precipitate IRIS, once the viral load is effectively suppressed (Narendran and Swaminathan, 2013). Endemic infections such as malaria, urinary tract infection, typhoid need to be routinely excluded. Chest X-ray provides not only valuable information in diagnosis but also to plan future management. Radiological deterioration in chest X-ray is a usual accompaniment in almost all cases of IRIS that occurs with proven pulmonary TB (Narendran *et al*, 2013). In some instances, CD4 cells may not increase in number immediately, but after a lag period (Narendran and Swaminathan, 2013). The detailed criteria for diagnosis of ART-associated TB (unmasking IRIS) and paradoxical IRIS were provided by the INSHI group (Meintjes *et al*, 2008). A negative culture of M.TB from the site of involvement, in an initially culture confirmed case of TB, is a definite indication of IRIS occurrence.

However, this criterion of culture negativity does not apply to the diagnosis of unmasking IRIS or in paradoxical IRIS when ATT-IRIS interval is extremely short.

The pre-ART (baseline) characteristics of patients that could be potential clinical and laboratory predictors of paradoxical IRIS are provided in Table 2 (Narendran *et al*, 2013).

The biomarkers that are significantly associated with IRIS prediction are depicted in Table 3. The values are after adjustment for age, time to ART, CD4 count, CD4/CD8 ratio and HIV RNA levels –pre-ART.

Differential diagnosis of IRIS

Emergence of drug-resistant TB and zidovudine-induced anaemia are the closest mimic of IRIS in India (Meintjes *et al*, 2008; Narendran and Swaminathan, 2013). Late-onset IRIS patients (occurring after 3 months of ART initiation) should have their viral load estimated once again to rule out ART failure and HIV progression (Colebunders *et al*, 2006). Lymphoma of the non-Hodgkins type which could occur in HIV or coexists with HIV may flare up with ART, and steroid administration alters the histopathological features, complicating diagnosis (Knysz *et al*, 2006).

Management of TB-IRIS

Preventive strategy. The recommendations of the WHO to start ART at a CD4 of <500 cells mm⁻³ and the National AIDS Control Organization to start ART irrespective of CD4 count in TB are effective preventive strategies against IRIS occurrence (WHO, 2014a,b). An interesting

Table 3 Immunological markers that are significant predictors of paradoxical IRIS

Candidate biomarker	adjusted OR (95% CI)	P value
IL-6 > 34.65 pg/mL	26.5 (5.1-136.6)	<0.0001
CRP > 6 mg/L	5.1 (1.5-17.7)	0.009
sFlt3-L > 350 pg/mL	5.6 (1.7-19.1)	0.005
sPD-1 > 1000 pg/mL	6.8 (2.2-21.2)	0.001
Ki67+PD-1+Treg > 40%	15.7 (5.2-47.6)	<0.0001
PD-1+CD8+Effm > 55%	9.8 (2.7-35.9)	0.001
Monocytes > 750/mL	4.6 (1.5-14.5)	0.010

fact is that long-term cotrimoxazole therapy prior to ART has been shown to reduce IRIS occurrence when compared to concurrently starting it with ART (Haddow *et al*, 2012). Intensive screening for TB and other opportunistic infections along with INH prophylaxis before ART initiation reduces IRIS incidence (Meintjes *et al*, 2008; Gopalan *et al*, 2014).

Treatment of TB-IRIS. Anti-inflammatory drugs, especially steroids from the main line of therapy for TB-IRIS (Gopalan *et al*, 2014). A dose of 0.5–2 mg kg⁻¹ body weight is usually used and tapered in a 4- to 8-week period depending on the site of disease. Premature

Table 2 Baseline differences between IRIS and non-IRIS patients – pre-ART

Characteristic	IRIS (N = 26)	Non-IRIS (N = 22)	P-value
Male gender	20 (76.9%)	18 (81.8%)	0.735
Age, median years (IQR)	36 (27–46)	37 (31–40)	0.967
Weight, median kg (IQR)	42.0 (36.0–48)	40.5 (35.7–46.5)	0.732
Time to ART, median days (IQR)	20 (14–30)	43 (23–68)	<0.001
Haematology			
Haemoglobin, median g dl ⁻¹ (IQR)	8.5 (7.1–10.2)	10.1 (9.0–11.3)	0.007
Hematocrit, median % (IQR)	25.5 (20.4–30.6)	29.2 (25.9–33.2)	0.007
RBC count, median ×10 ⁶ per ml (IQR)	3.47 (2.8–3.8)	3.9 (3.2–4.1)	0.087
CD4 ⁺ T cells per μl, median (IQR)	93 (39–135)	156 (89–264)	0.005
CD8 ⁺ T cell per μl, median (IQR)	765 (311–1095)	459 (297–727)	0.109
CD4/CD8 ratio, median (IQR)	0.09 (0.05–0.18)	0.34 (0.21–0.47)	<0.001
HIV RNA, median log ₁₀ copies per ml plasma (IQR)	5.9 (5.4–5.9)	5.3 (4.5–5.6)	<0.001
Plasma biochemistry			
ALT, median IU l ⁻¹ (IQR)	30.5 (14.0–52.2)	30.5 (13.5–45.7)	0.868
AST, median IU l ⁻¹ (IQR)	54.5 (30.5–91.7)	35.0 (22.7–62.2)	0.102
TB evaluation			
Sputum smear grade			0.515
1+	13 (50%)	8 (36.4%)	
2+	9 (34.6%)	8 (36.4%)	
3+	4 (15.4%)	6 (27.2%)	
Sputum culture grade			0.002
1+	6 (23.0%)	3 (13.7%)	
2+	10 (38.5%)	5 (22.7%)	
3+	10 (38.5%)	14 (63.6%)	
Number of chest X-ray zones, median (IQR)	3 (2–5)	3 (2–5)	0.824
Presence of EPTB site	19 (73.1%)	7 (31.8%)	0.004
Presence of miliary TB	12 (46.1%)	3 (13.6%)	0.012

ALT, alanine transaminase; AST, aspartate aminotransferase; ATT, anti tuberculous treatment; EPTB, extra-pulmonary tuberculosis; IQR, interquartile range; RBC, red blood cell; TB, tuberculosis.

Data represent no. (%) of participants unless otherwise specified.

withdrawal of steroids may result in recrudescence of symptoms (Narendran and Swaminathan, 2013; Narendran *et al*, 2013). Severe forms may require parenteral steroids initially followed by switch to oral steroids. Thalidomide (Brunel *et al*, 2012) in steroid-dependent IRIS has been tried, so are anecdotal reports of pentoxifylline, montelukast (a leukotriene inhibitor) (Lipman *et al*, 2007). The CADIRIS trial proved beyond doubt that maraviroc was not useful in preventing IRIS (Sierra-Madero *et al*, 2013) Research is required in order to choose specific blocking agents to inflammatory mediators such as IL-6, IL-18, CXCR3, CD28 monoclonal antibody instead of non-specific anti-inflammatory agents such as steroids, which will be most useful in an already weakened but recovering immune system.

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