EXPERT REVIEWS

# Coping with TB immune reconstitution inflammatory syndrome

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The TB immune reconstitution inflammatory syndrome (IRIS) is a relatively frequent complication in HIV–TB-coinfected patients after they start highly active antiretroviral therapy (HAART). There are two forms of TB IRIS: the 'paradoxical' type (clinical worsening of a patient on TB treatment) and the 'unmasking' type (undiagnosed TB becoming apparent after starting HAART). Their pathogeneses are not fully understood, although, as the name suggests, IRIS following initiation of HAART is accompanied by an increase in immune responses to *Mycobacterium tuberculosis*. The diagnosis of TB IRIS is mainly clinical; so far there are no laboratory tests able to diagnose or predict TB IRIS. Risk factors for TB IRIS include a low CD4+ lymphocyte count, disseminated TB infection at HAART initiation and a short interval between TB treatment and HAART initiation. TB IRIS complicates the treatment and care for HIV–TB-coinfected patients. In this paper, we discuss some aspects of pathogenesis and options for the treatment and prevention of TB IRIS.

**Keywords:** • HAART • highly active antiretroviral therapy • HIV • immune reconstitution inflammatory syndrome • immune restoration disease • TB

The TB–HIV copandemic represents a convergence of two debilitating chronic illnesses [1–3]. The treatment of both diseases demands multiple drug therapies [4] and good adherence to treatment. This may not always be feasible due to multiple or cumulative adverse effects and toxicities arising from this combined therapy but also because of immunological reactions arising from the initiation of highly active antiretroviral therapy (HAART). Initially described in HIV patients on zidovudine who had restoration of cutaneous delayed-type hypersensitivity to TB [5], the immune reconstitution inflammatory syndrome (IRIS), or immune restoration disease, is associated with the start of antiretroviral therapy in patients with severe immune suppression and underlying opportunistic diseases [6,7]. This syndrome occurs in the context of many opportunistic infections early during the course of antiretroviral therapy and affects multiple organ systems but is particularly common among patients with TB and HIV [8,9].

There are two types of TB IRIS. First, there is paradoxical TB IRIS. In this type of IRIS, there is worsening of TB after starting antiretroviral therapy. The second form is known as unmasking TB. In this situation, TB arises as a diagnosis for the first time in someone taking antiretroviral therapy in whom TB was previously undiagnosed or subclinical. Both types of IRIS are as a result of the restoration of pathogen-specific immune responses during the initial months of HAART when the host's immunopathological responses are 'switched on' [10–12]. 'HAART-associated TB' has been used to refer to all patients with a new episode of TB while on HAART. Unmasking TB IRIS refers only to those who have overt signs and symptoms of inflammation out of proportion to the usual presentation of TB disease [11]. The diagnosis of this disorder is mainly clinical and its pathogenesis is not fully understood. Currently, there are no specific laboratory tests available to diagnose or predict TB IRIS.

## Case illustration

A 35-year-old HIV-seropositive male with a CD4+ lymphocyte count of 49 cells/µl was admitted because of cough, chest pain, night sweats and poor appetite. A clinical examination revealed bilateral submandibular and axillary lymphadenopathy. He was diagnosed as having extrapulmonary TB (based on clinical and sonographic evidence). The abdominal ultrasound scan revealed lymphadenopathy involving the

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mesenteric and para-aortic groups and microsplenic abscesses. At baseline he had a normal chest x-ray evaluation, and two sputum examinations for acid-fast bacilli were negative.

After 6 weeks of TB treatment, the patient started HAART with zidovudine, lamivudine and efavirenz. At the time of HAART initiation, the TB-related symptoms had subsided. However, submandibular and axillary lymphadenopathy were still noted.

A total of 2 months after HAART initiation, the patient developed chills, poor appetite and abdominal pain. On physical examination, he had submandibular and axillary lymphadenopathy. He also had periumbilical and epigastric tenderness.

Over the next 2 weeks, the neck swellings progressively increased in size but remained painless (Figure 1). An ultrasound of the neck showed bilateral multiple hypoechoic, semisolid masses on both sides of the neck; the largest were 4.14 × 2.7 cm on the left and 3.9 × 2.4 cm on the right. An abdominal ultrasound scan showed multiple enlarged nodes: para-aortic glands in the region of the portahepatis, mesenteric lymph nodes, parailiac lymph nodes, peripancreatic lymph nodes and splenic abscesses.

An initial aspiration of the cervical swellings yielded 6 ml of pus. On Ziehl–Nielsen stain, four acid-fast bacilli per 100 high-power fields were seen, but there was no growth on mycobacterial culture. Over a period of 1.5 months the patient had six needle aspirations of the neck swellings (Figure 2). A total of approximately 300 ml of pus was aspirated. At each drainage, the patient experienced relief in symptoms. The neck swellings gradually reduced in size, although some residual cervical lymphadenopathy persisted. All other clinical symptoms of this episode of paradoxical TB IRIS resolved without a change in the patient's treatment. Additional therapy consisted of nonsteroidal anti-inflammatory analgesics.

## Epidemiology & pathogenesis

Immune reconstitution inflammatory syndrome is caused by an unbalanced or exaggerated activation of the immune system during immune reconstitution on HAART against antigens from living or dead pathogens [12–14]. TB IRIS has been observed to occur more often in patients with a greater severity of illness [15,16]. The association of this syndrome with advanced HIV-related immune deficiency and $CD4^+$ lymphocyte counts has also been noted and occurs especially when the patients start HAART close to the time of diagnosis of TB or other opportunistic infections [17,18]. From animal models, epidemiologic studies and clinical observations, TB IRIS is prominently associated with extrapulmonary and disseminated TB infection [19,20]. Although difficult to measure *in vivo*, it is also likely that a high mycobacterial load is a risk factor for TB IRIS. This has been demonstrated in animal models by Manabe *et al.* [19]. Patients who develop TB IRIS often demonstrate a prompt response to HAART with an increase in $CD4^+$ lymphocyte counts, although they may develop it even before significant increases in $CD4^+$ lymphocyte counts occur, especially while on potent HAART regimens, resulting in a rapid decline in viral load [17,21]. Other risk factors have been reported, such as a high CD8 percentage, a high viral load, and an unbalanced restoration of Th17 lymphocytes and regulatory T cells [10,22], and protease inhibitor-based regimens [21,23]. However, additional studies are needed to confirm these findings. A recent study revealed that higher anti-PGL-Tb1 antibody levels were identified in HIV–TB-coinfected patients who did not develop IRIS compared with TB IRIS patients. The presence of specific anti-PGL-Tb1 antibodies could therefore be an indicator of a potentially protective response or a diagnostic biomarker for the detection of nonprogression to TB IRIS in HIV–TB-coinfected patients starting HAART [24].

Recently, some teams have oriented their research to killer immunoglobulin-like receptors (KIRs). KIRs are a family of cell-surface molecules expressed by natural killer cells and some populations of CD8 T cells. The consequences of interactions between cytotoxic cells and virus-infected cells are determined by the expression of inhibitory and activating KIRs [25]. Bourgarit and others recently identified an association of TB IRIS with an increase of activated tuberculin-specific effector-memory CD4 T cells and of $V\delta2^+KIR\text{-}\gamma\delta^+$ T cells before the start of HAART [26].

A major limitation in understanding the epidemiology and pathogenesis of TB IRIS was the lack of a universally accepted case definition of TB IRIS [8,9]. Moreover, many of the initial studies were retrospective in design or were case series and reports. There was also no consensus on the definitions suggested. Recently, a case definition was proposed that can be used in both low- and high-income settings [27]. There are three components (A, B and C) to this case definition. These are shown in Box 1.

The case definition for unmasking TB IRIS is shown in Box 2. Researchers in the field are encouraged not to regard all patients with HAART-associated TB as having TB IRIS, but only those that fit this provisional unmasking TB IRIS case definition. However, critical evaluation of the clinical spectrum of patients developing HAART-associated TB will assist with refinement of this case definition in the future. Diagnostic imaging is useful for diagnosis, monitoring of disease progress

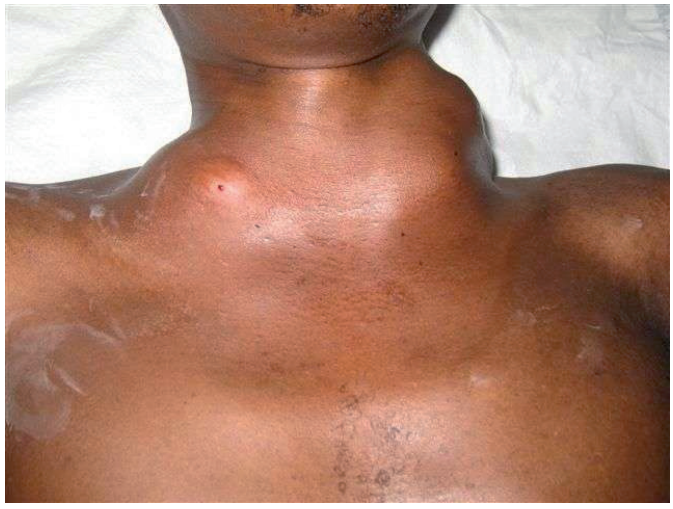

**Figure 1. Bilateral massively enlarged cold abscesses in the neck of a patient with TB immune reconstitution inflammatory syndrome.**

and management of the complications of TB IRIS. Radiological features should be viewed in the context of clinical and pathological findings as part of the multidisciplinary approach to making a diagnosis.

## Impact of TB IRIS

The socioeconomic impact of TB IRIS has not yet been fully assessed but its occurrence is associated with multiple clinic visits and an increased risk of hospitalization in some patients [9]. Patients may need additional investigations and treatments that are not routinely available. In most resource-constrained settings without health insurance schemes, the responsibility for healthcare is borne by the state, specialized investigations are not routinely available free of charge and the financial burden is shifted to the patients and relatives. The occurrence of TB IRIS may also directly affect adherence to both antiretroviral therapy and TB treatment. Reports of people suffering from worsening of symptoms after starting HAART treatment contribute to the reluctance of some patients to initiate antiretroviral therapy and their lack of confidence in the healthcare system.

For most health units, management of patients with TB IRIS is complicated, diagnostic tools are generally lacking and it is difficult to exclude other conditions such as treatment failure, drug toxicity or another comorbidity [28]. The decision to refer for hospitalization or not is also difficult since health personnel may not be well informed about the presentation of TB IRIS. Furthermore, there are no clear guidelines on how to manage TB IRIS. This can impact negatively on the present efforts to decentralize HAART provision services, since a lack of the necessary infrastructure compromises the quality of HIV and TB care.

## Treatment possibilities

In South Africa, a placebo-controlled, randomized trial evaluating the use of steroids has just been completed and preliminary results indicate that the use of prednisone reduces the need for hospitalization and procedures, and results in symptom improvement without an excess of corticosteroid side effects or severe infections [29]. However, drug-resistant TB and other causes for deterioration must be ruled out before treatment. The use of nonsteroidal anti-inflammatory drugs and thalidomide in the treatment of these patients has also been suggested, and there is a report suggesting that leukotriene antagonists may be beneficial in the treatment of TB IRIS [30].

## Prevention of TB IRIS

It is still not clear how to predict who will develop TB IRIS. Low $CD4^+$ lymphocyte count at HAART initiation is a major risk factor for TB IRIS [21,31]. Starting HAART at a higher $CD4^+$ lymphocyte count, before opportunistic infections appear, is probably the best way to prevent the occurrence of TB IRIS. This calls for improvement of access to $CD4^+$ lymphocyte count testing facilities for all patients who test positive for HIV. However, at present, the majority of HIV-infected individuals, especially in low-resource settings, do not know their serostatus [32,33]. Most patients therefore present late to health units with advanced HIV immunosuppression and opportunistic infections. Universal access to HIV-testing facilities and routine $CD4^+$ lymphocyte count testing in patients diagnosed with HIV will help to detect patients eligible for HAART earlier.

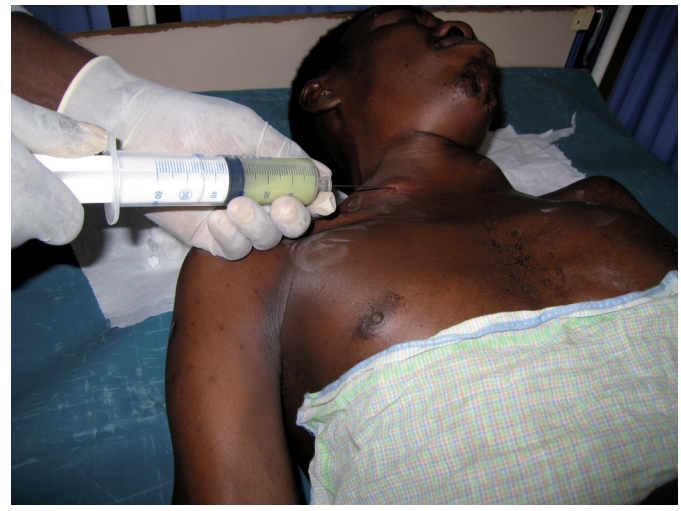

**Figure 2. Diagnostic and therapeutic aspiration of cold abscesses in a TB immune reconstitution inflammatory syndrome patient.**

Isoniazid prophylaxis has been shown to prevent the development of active TB in HIV-infected patients [34] and therefore may reduce the risk of TB IRIS. This, however, presents significant diagnostic and logistical limitations that restrict its applicability. It is difficult to distinguish latent TB infection (LTBI) from active disease using the available diagnostic tests. In the context of HIV, anergy to tuberculin compromises the value of Mantoux skin testing in screening for LTBI. Recent γ-interferon release assays, which quantify antigen-specific T lymphocytes (enzyme-linked immunosorbent spot [ELISpot] and quantiferon assays) are more specific than skin tests but are not readily available for use in programmatic settings. A recent metanalysis by Menzies and others found QuantiFERON® and ELISpot showed excellent sensitivity, while ELISpot was more sensitive than tuberculin skin testing (TST) in a few studies [35]. A cross-sectional study in a low HIV/TB-prevalence setting indicated poor concordance between ELISpot, QuantiFERON and TST results [36]. Further prospective studies are needed to address the role of these tests in high-burden HIV/TB countries. Injudicious use of isoniazid preventive therapy on a widescale level could predispose to the development of isoniazid resistance, which may further compound the problem of TB drug resistance.

Finally, the occurrence of IRIS has been linked to high mycobacterial antigen load in animal models [19]. Unfortunately, the measurement of antigenic load in human populations is difficult, although disseminated TB has been identified as a risk factor for TB IRIS [37]. When better diagnostic tests are available to screen for TB in HIV-infected populations, early diagnosis and treatment of TB, before patients are eligible for HAART, could prevent the occurrence of TB IRIS.

**Box 1. Case definition for paradoxical TB immune reconstitution inflammatory syndrome.**

*A) Antecedent requirements*

Both of the following requirements must be met:

- **Diagnosis of TB:** the TB diagnosis was made before starting HAART and this should fulfill WHO criteria for diagnosis of smear-positive PTB, smear-negative PTB or extrapulmonary TB
- **Initial response to TB treatment:** the patient's condition should have stabilized or improved on appropriate TB treatment prior to HAART initiation – for example, cessation of night sweats, fevers, cough and weight loss (note: this does not apply to patients starting HAART within 2 weeks of starting TB treatment as insufficient time may have elapsed for a clinical response to be observed)

*B) Clinical criteria*

The onset of TB IRIS manifestations should be within 3 months of HAART initiation, reinitiation or regimen change due to treatment failure

Of the following, at least one major criterion or two minor clinical criteria are required:

- **Major criteria**
  - New or enlarging lymph nodes, cold abscesses or other focal tissue involvement (e.g., TB arthritis)
  - New or worsening radiological features of TB (using chest radiography, abdominal ultrasonography, CT or MRI)
  - New or worsening CNS TB (meningitis or focal neurological deficit, e.g., due to tuberculoma)
  - New or worsening serositis (pleural effusion, ascites or pericardial effusion)
- **Minor criteria**
  - New or worsening constitutional symptoms, such as fever, night sweats or weight loss
  - New or worsening respiratory symptoms, such as cough, dyspnea or stridor
  - New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly or abdominal adenopathy

*C) Alternative explanations for clinical deterioration must be excluded if possible**

- Failure of TB treatment due to TB drug resistance
- Poor adherence to TB treatment
- Another opportunistic infection or neoplasm (it is particularly important to exclude an alternative diagnosis in patients with smear-negative PTB and extrapulmonary TB where the initial TB diagnosis has not been microbiologically confirmed)
- Drug toxicity or reaction

*It may be difficult or impossible in resource-poor settings to confirm TB drug resistance and to exclude certain other infections or neoplasia. Cases where alternative diagnoses cannot be fully excluded because of limited diagnostic capacity should be regarded as 'probable paradoxical TB IRIS'. In these probable cases, should resolution of clinical or radiological findings of the suspected IRIS episode occur without a change in TB treatment or HAART having been made, they could then be reclassified as 'paradoxical TB IRIS' cases.

HAART: Highly active antiretroviral therapy; IRIS: Immune reconstitution inflammatory syndrome; PTB: Pulmonary TB.

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Cotrimoxazole prophylaxis has been shown to be beneficial in patients being treated for both TB and HIV. It is not clear how much this intervention contributes to the prevention of IRIS.

## Expert commentary

Tuberculosis IRIS is a big challenge for the roll-out of antiretroviral treatment. It causes confusion to healthcare providers and is difficult to differentiate from drug toxicity, disease progression, concomitant infection and drug resistance.

More research is required to identify predictive markers and biological parameters of TB IRIS. It is also important to accurately document the mortality and economic burden of TB IRIS. Randomized trials on the treatment and prevention of IRIS are urgently needed.

## Five-year view

In the next few years, we will gain an improved understanding of the underlying pathogenesis of TB IRIS. However, in order to decrease the incidence of TB IRIS, earlier diagnosis and treatment of TB and HIV will be critical. The current worldwide efforts to scale-up HIV testing, to screen for TB among persons with HIV infection and to increase the access to basic care and HAART will reduce the incidence of TB and TB IRIS.

It is important to address pertinent issues raised by TB IRIS. Randomized, controlled trials are underway to address when to start HAART in patients with opportunistic infections, such as TB [38] and cryptococcosis. Biological markers that predict IRIS would assist in the rapid identification of patients at risk of TB IRIS.

**Box 2. Case definition for unmasking immune reconstitution inflammatory syndrome.**

The patient is not receiving treatment for TB when HAART is initiated and then presents with active TB within 3 months of starting HAART and heightened intensity of clinical manifestations, particularly if there is evidence of a marked inflammatory component to the presentation. Examples include TB lymphadenitis or TB abscesses with prominent acute inflammatory features, presentation with pulmonary TB that is complicated respiratory failure due to adult respiratory distress syndrome and those who present with a marked systemic inflammatory syndrome related to TB.

HAART: Highly active antiretroviral therapy.

Patients identified using these criteria could then be targeted with interventions, some of which have adverse effects. Prospective studies of the prevention and treatment of TB IRIS will provide the opportunity to investigate the pathogenesis of TB IRIS and the mechanisms of this disease spectrum.

Within 3 months of HAART initiation, many patients with TB–HIV coinfection die in resource-constrained settings. This may be due to progression of the underlying disease or may be due to IRIS, especially with comorbid illnesses or CNS inflammation. The contribution of TB IRIS to this unacceptably high mortality rate must be investigated.


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## Key issues

- TB immune reconstitution inflammatory syndrome (IRIS) is a relatively frequent complication in HIV–TB-coinfected patients after starting highly active antiretroviral therapy (HAART); (up to 20% within 3 months of starting HAART in TB-endemic areas).
- IRIS results from an exaggerated immune reconstitution against living or dead pathogens.
- There are two forms of TB IRIS: the paradoxical type (clinical worsening of a patient on TB treatment) and the unmasking type (undiagnosed TB becomes apparent after starting HAART).
- Risk factors include a low $CD4^+$ lymphocyte count, disseminated TB at HAART initiation and a short interval between the start of TB treatment and HAART. Other risk factors that need further investigation are a high CD8 percentage, a high viral load, an unbalanced restoration of Th17 lymphocytes and regulatory T cells, and a protease inhibitor-based regimen. Recently, a link was suggested between IRIS and a low antiphenolic gylcolipid-Tb1 antibody level, as well as an increase of activated tuberculin-specific effector memory CD4 T cells and of $Vd2^+$ killer immunoglobulin receptor-$gd^+$ T cells, before the start of HAART.
- The diagnosis of TB IRIS is mainly clinical; currently, there is no specific laboratory test able to diagnose or predict TB IRIS.
- There are no guidelines for prevention and treatment of TB IRIS. Prednisone is beneficial for the care of IRIS, but drug-resistant TB and other causes for deterioration must be ruled out before use. Despite the proven efficacy of isoniazid and cotrimoxazole to prevent morbidity and mortality due to TB, their role in the prevention of TB IRIS is not known.

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