



## Tuberculosis-immune reconstitution inflammatory syndrome



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### ABSTRACT

Tuberculosis-immune reconstitution inflammatory syndrome is an excessive immune response against Mycobacterium tuberculosis that may occur in either HIV-infected or uninfected patients, during or after completion of anti-TB therapy. In HIV-infected patients it occurs after initiation of antiretroviral therapy independently from an effective suppression of HIV viremia. There are two forms of IRIS: paradoxical or unmasking. Paradoxical IRIS is characterized by recurrent, new, or worsening symptoms of a treated case. Unmasking IRIS is an antiretroviral-associated inflammatory manifestation of a subclinical infection with a hastened presentation. The pathogenesis is incompletely understood and the epidemiology partially described. No specific tests can establish or rule out the diagnosis. Treatment is based on the use of anti-tuberculosis drugs sometime with adjunctive corticosteroids. Mortality is generally low.

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### Introduction

Tuberculosis-immune reconstitution inflammatory syndrome (TB-IRIS) is an abnormal, excessive immune response against alive or dead Mycobacteria tuberculosis that may occur in either HIV-infected or, more rarely, uninfected patients. In HIV-infected patients it occurs after initiation of antiretroviral therapy independently of an effective suppression of HIV viremia. Paradoxical worsening of tuberculosis in HIV-uninfected patients was indeed first described after introduction of antituberculous drugs in 1954 [1]. This review summarizes the available literature on epidemiology, pathogenic mechanisms, diagnosis, clinical manifestations, and treatment options of TB-IRIS.

### Definition of TB-IRIS

TB-IRIS is a paradoxical worsening or recurring of preexisting tuberculous lesions, or a development of new lesions in patients on effective antituberculosis treatment. It may occur during or even after completion of anti-TB therapy. TB-IRIS might be misdiagnosed as superimposed infections, treatment failure following inadequate anti-TB treatment, drug-resistant TB, or TB relapse [2, 3]. Therefore, the following strict criteria must be applied to diagnose TB-IRIS [4]:

- (1) initial improvement of TB-related symptoms and/or radiographic findings after adequate anti-TB treatment for a certain time;
- (2) paradoxical deterioration of TB-related symptoms and/or radiologic findings at the primary or at new locations during or after anti-TB treatment;
- (3) absence of conditions that reduce the efficacy of anti-TB drugs (e.g., poor compliance, drug malabsorption, drugs side effects);
- (4) exclusion of other possible causes of clinical deterioration.

In an attempt to develop diagnostic criteria, various definitions of IRIS were developed in HIV-infected patients, including those proposed by Shelburne et al. [5], French et al. [6], and Robertson et al. [7]. In 2008 a consensus definition for TB-associated IRIS was created for resource poor-settings [8] in order to have a standardized case definition which could assist in diagnosing TB-IRIS in countries with limited resources.

There are two forms of IRIS: paradoxical or unmasking. Paradoxical IRIS is defined as recurrent, new, or worsening symptoms of a treated case. Unmasking IRIS is an antiretroviral (ART)-associated inflammatory manifestation of a subclinical infection with a hastened presentation. In this latter form signs and symptoms not clinically apparent before, appear during ART.

### Epidemiology

Different studies have estimated the frequency of TB-IRIS between 2% and 23% [3,9,10–13] in HIV-uninfected patients. In

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HIV-infected patients a retrospective meta-analysis of 54 cohorts showed that the incidence of TB-IRIS in patients on ART treatment was 15.7% with a mortality of 3.2% [14]. Neurological TB-IRIS occurred in 12% of TB-IRIS cases in a single center in a TB endemic area [15]. Nonetheless the frequency of tuberculosis-associated IRIS remains difficult to assess because of the heterogeneity of the definitions. Risk factors for a paradoxical response include disseminated tuberculosis [8], young age, male gender, anemia [4], lymphopenia or a CD4+ T lymphocyte count less than 50/mm<sup>3</sup>, use of biological agents (e.g., anti-TNF $\alpha$ ), and a marked increase in lymphocyte count or suppression of HIV-RNA replication with antiretroviral therapy [8,13]. The median time to onset of the paradoxical response was 21–56 days after initiation of antituberculous treatment in HIV-uninfected patients [13], and two–four weeks in HIV-infected patients on antiretroviral therapy [8]. The overall mortality in patients with a paradoxical response has been estimated at 3% [14].

### Pathogenesis

The immunopathogenesis of IRIS remains only partially understood. Qualitative and quantitative reconstitution of the immune system, host genetic susceptibility and mycobacterial load are supposedly involved in the pathogenesis of IRIS.

The role of the amount of mycobacteria in the pathogenesis is suggested by several observations. In patients with disseminated or extrapulmonary tuberculosis the increased risk of IRIS is attributed to a higher bacillary load [2,3]. In HIV-positive patients, the risk of IRIS is highest if the antiretroviral therapy is initiated early during antimycobacterial treatment, when the mycobacterial load is considerable [16], as shown in trials trying to establish the correct time of ART initiation [17–19].

The hasty killing of mycobacteria by anti-TB therapy may determine the release of large amounts of mycobacterial antigens, which can stimulate an excessive inflammatory response [20]. A prospective study recently showed a correlation between positive sputum culture (indicating high antigenic load) and inflammatory monocyte activation markers (strongly predictive of development of paradoxical TB-IRIS), suggesting that high antigen loads and inflammation may act together in the pathogenesis [21]. However host inflammatory responses (with the release of proinflammatory cytokines) may be stronger determinants of IRIS pathogenesis than mycobacterial factors [22]. Other studies also indicate that immune reconstitution is involved in the pathogenesis of IRIS, and in particular the reconstitution of T helper 1 CD4+ immune responses, as shown by the conversion of tuberculin skin tests to positive after treatment start [2,11]. ART initiation has been associated with a shift from T helper 2 to T helper 1 cytokine patterns, and with the restoration of T lymphocyte proliferative responses [23].

In conclusion, the immunopathogenesis of IRIS in both HIV-infected and uninfected patients appears to involve T helper 1-driven immune responses in the presence of multibacillary disease and immunodeficiency.

### Clinical manifestations

TB-IRIS in HIV-uninfected patients is more frequent in extrapulmonary (especially in pleural and lymph node forms) than in pulmonary TB. The median time to IRIS onset after starting anti-TB drugs is generally up to three months. The most frequent presenting symptoms of TB-IRIS are recurrent fever, enlarged lymph nodes and worsening dyspnea [2]. The principal sites involved in TB-IRIS are lymph nodes (68%) and lungs (16%), independently of the sites of primary tuberculosis [4]. Thoracic TB-IRIS manifest as

new pulmonary parenchymal lesions [24,25], development of new lymphadenopathy or increase in the size of a preexisting lymphadenopathy [2,9,25,26], development of new or progression of preexisting pleural effusions [27,28], new endobronchial lesions. TB-IRIS usually develops on the same side of primary TB, though contralateral or bilateral lesions can also occur [24].

Development of new lymphadenopathy or enlargement of preexisting lymph nodes can be observed in up to 25% of HIV-uninfected patients with peripheral TB lymphadenitis [3]. The median time to development is generally 4–14 weeks after the initiation of anti-TB treatment but can also be longer (1–13 months after treatment completion) [9,26]. In patients with pleural TB new peripheral pulmonary lesions occur in 2.4%–11%, developing 1–9 months after the beginning of anti-TB therapy [25].

Pleural TB-IRIS (manifesting as a new or increased pleural effusion) happens in 16%–45% of HIV-uninfected patients with pleural [27,28], lymph node [25], or pulmonary TB [3]. It generally develops within 3–19 weeks of treatment initiation [28].

In patients with miliary or disseminated TB the occurrence of soft tissue TB-IRIS (presenting as new inflammatory or non-inflammatory lesions within the skin or subcutaneous tissues) is more frequent than in those with pleural or lymph node TB [29, 30]. Endobronchial TB-IRIS, manifesting as partial or totally obstructive lesions, is rare and can be due either to a fistulation or erosion of a lymph node into a bronchus or a *de novo* endobronchial reaction [31].

TB-IRIS in HIV-infected patients is one of the most common forms of IRIS and occurs in 15.7% of TB patients starting ART according to Müller's meta-analysis [14]. However some studies report higher rates; for instance, a 54.2% incidence was reported in patients with culture-confirmed pulmonary TB in India [32], and a 47% incidence of paradoxical TB-IRIS was found in South African patients with TB meningitis [15], determining a considerable disease burden [33].

Although both paradoxical and unmasking forms of TB-IRIS have been reported in HIV-infected individuals, paradoxical IRIS has been more extensively and better studied. In patients with pulmonary tuberculosis, paradoxical TB-IRIS presents as a worsening or recurrence of respiratory (shortness of breath, cough) and constitutional symptoms (fever, weight loss, night sweats), and often new or expanding infiltrates on chest X-ray images [34]. Lymph node paradoxical IRIS generally presents with rapid enlargement followed by suppuration [35].

Paradoxical neurologic TB-IRIS is a possibly life threatening condition and symptoms tend to manifest later than in forms not involving the central nervous system, generally 5–10 months after ART initiation. Neurologic TB-IRIS generally presents with new or worsening meningitis and/or features of raised intracranial pressure, due to enlarging cerebral tuberculomas or intracranial abscesses; mortality is high and ranges from 12% to 25% [36–38]. It may also present with spondylitis, epidural abscesses, and radiculomyelopathy [15,38].

Abdominal TB-IRIS can occur as granulomatous hepatitis, retroperitoneal lymphadenopathy, and peritonitis, whereas the musculoskeletal form manifests as mono- or polyarthritis [39].

'Unmasking TB-IRIS' is not as well defined as "paradoxical TB-IRIS" and refers to a form of TB that becomes clinically recognizable after the initiation of ART and presents with exaggerated inflammatory features. It usually develops within the first three months of ART. Unmasking TB-IRIS forms can vary widely in the degree of clinical presentation, often with features indistinguishable from those of paradoxical TB-IRIS. Two-thirds of unmasking forms present with lung involvement (often severe pulmonary tuberculosis leading to acute respiratory distress syndrome, or bronchiolitis obliterans organizing pneumonia) [40, 41].

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