

Immune Reconstitution Inflammatory Syndrome Generic Criteria

- 1. Initiation, reintroduction or change in antiretroviral therapy/regimen or therapy for opportunistic infections (OI).**

AND

- 2. ¹Evidence of:**
 - a. an increase in CD4+ cell count as defined by ≥ 50 cells/mm³ or a ≥ 2 - fold rise in CD4+ cell count, and/or**
 - b. decrease in the HIV-1 viral load of >0.5 log₁₀ and/or**
 - c. weight gain or other investigator-defined signs of clinical improvement in response to initiation, reintroduction or change of either antiretroviral therapy/regimen or OI therapy.**

AND

- 3. Symptoms and/or signs that are consistent with an infectious or inflammatory condition.**

AND

- 4. These symptoms and/or signs cannot be explained by a newly acquired infection, the expected clinical course of a previously recognized infectious agent, or the side effects of medications.**

¹ If the study participant is being evaluated for an inflammatory condition at a time that is <4 weeks after initiation, reintroduction or change in antiretroviral therapy/regimen or OI therapy, items 2a through 2c are not required.

Criteria for the Diagnosis of Tuberculosis Specific Immune Reconstitution Inflammatory Syndromes (TB-IRIS)

Tuberculosis-associated IRIS can present as one of two main syndromes:

1. A paradoxical reaction after the start of ART in patients receiving tuberculosis treatment (“**paradoxical**” tuberculosis-associated IRIS), or
2. A new presentation of tuberculosis that is “unmasked” in the weeks following initiation of ART with an exaggerated inflammatory clinical presentation or complicated by a paradoxical response (“**unmasking**” tuberculosis associated IRIS).

A “paradoxical” response to anti-tuberculous therapy was described as far back as 1955 in patients initiating therapy. In the HAART era, IRIS associated with TB is common and occurs in approximately 8-43% and typically consists of new and persistent fever after starting antiretroviral therapy/regimen; worsening or emergence of intrathoracic adenopathy, pulmonary infiltrates or pleural effusions, or worsening or emergence of cervical nodes on serial exam or of other tuberculous lesions, such as skin and CNS. It usually occurs within the first 4 weeks of beginning antimycobacterial therapy with or without antiretroviral therapy/regimen but has been described as late as 9 months when the patient is smear-negative. Antiretroviral therapy/regimen can usually be continued, often with anti-inflammatory support; corticosteroids have been used in those with CNS lesions or who are critically ill [1-6].

Confirmed TB IRIS in patients *with* a prior history of TB (**paradoxical** TB-associated IRIS):

There are three components to this case-definition (adopted from Lancet Infect Dis 2008, reference 6):

A) Antecedent requirements

- i) Diagnosis of tuberculosis: previous pulmonary (smear positive or smear-negative) or extrapulmonary TB diagnosis

AND

- ii) Initial response with anti-TB therapy (i.e. stabilization or improvement of signs/symptoms with appropriate anti-TB therapy prior to initiation of ART)*. For example there has been cessation or improvement of fevers, cough, night sweats.

* (Note: this does not apply to patients starting ART within 2 weeks of starting tuberculosis treatment since insufficient time may have elapsed for a clinical response to be reported)

B) Clinical criteria

The onset of tuberculosis-associated IRIS manifestations should be within 3 months of ART initiation, reinitiation, or regimen change because of HIV 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. tuberculous arthritis

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Definitions of TB-IRIS

- New or worsening radiological features of tuberculosis (found by chest radiography, abdominal ultrasonography, CT, or MRI)
- New or worsening CNS tuberculosis (meningitis or focal neurological deficit; e.g. caused by 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

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

Confirmed TB IRIS in patients *without* a prior history of TB (ART “unmasking” TB-associated IRIS):

- Patient is not receiving treatment for TB when ART is initiated.
- Active TB is diagnosed after initiation of ART
- Active TB develops within 3 months of starting ART and one of the following criteria is met:
 - Heightened intensity of clinical manifestations, particularly if there is evidence of a marked inflammatory component. For example, presentations may include TB lymphadenitis or TB abscesses with prominent acute inflammatory features;
 - The development of pulmonary* or extrapulmonary TB with no evidence of miliary disease accompanied by marked focal inflammation; or
 - Histopathology from involved site demonstrating inflammatory changes (e.g., granulomas, caseation) accompanied by histologic or culture evidence of AFB consistent with TB in the absence of positive cultures for any other AFB.

Probable TB IRIS in patients *with* a prior history of TB (paradoxical TB-associated IRIS)

“Probable” status should be assigned for cases where criteria A and B are met (see confirmed TB IRIS with a prior history of TB definition) but an alternative diagnosis or explanation for clinical deterioration cannot be fully excluded.

Probable TB IRIS in patients *without* a prior diagnosis of TB (ART “unmasking” TB-associated IRIS)

- Patient is not receiving treatment for TB when ART is initiated
- Active TB is diagnosed after initiation of ART
- There is heightened intensity of clinical manifestations but there is not clear evidence of a marked inflammatory component to the presentation or the subsequent development of focal inflammatory site(s) is beyond 3 months of ART initiation.

References

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