Lancet Infect Dis. Author manuscript; available in PMC 2010 January 10.

Published in final edited form as:
Lancet Infect Dis. 2008 August ; 8(8): 516–523. doi:10.1016/S1473-3099(08)70184-1.

Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings

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Abstract

The immune reconstitution inflammatory syndrome (IRIS) has emerged as an important early complication of antiretroviral therapy (ART) in resource-limited settings, especially in patients with tuberculosis. However, there are no consensus case definitions for IRIS or tuberculosis-associated IRIS. Moreover, previously proposed case definitions are not readily applicable in settings where laboratory resources are limited. As a result, existing studies on tuberculosis-associated IRIS have used a variety of non-standardised general case definitions. To rectify this problem, around 100 researchers, including microbiologists, immunologists, clinicians, epidemiologists, clinical trialists, and public-health specialists from 16 countries met in Kampala, Uganda, in November, 2006. At this meeting, consensus case definitions for paradoxical tuberculosis-associated IRIS, ART-associated tuberculosis, and unmasking tuberculosis-associated IRIS were derived, which can be used in high-income and resource-limited settings. It is

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Conflicts of interest We declare that we have no conflicts of interest.

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envisaged that these definitions could be used by clinicians and researchers in a variety of settings to promote standardisation and comparability of data.

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Introduction

The immune reconstitution inflammatory syndrome (IRIS; also known as immune reconstitution disease, immune reconstitution syndrome, or immune restoration disease) is a widely recognised phenomenon that can complicate antiretroviral therapy (ART).1,2 The condition results from rapid restoration of pathogen-specific immune responses to opportunistic infections, causing either the deterioration of a treated infection or the new presentation of a previously subclinical infection. IRIS typically occurs during the initial months of ART and is associated with a wide spectrum of pathogens, most commonly mycobacteria, herpes-viruses, and deep fungal infections such as cryptococcal meningitis.[1–3]

In recent years, access to ART has increased rapidly in resource-limited settings, reaching over 2 million people by December, 2006, with an estimated 1 340 000 of these individuals living in sub-Saharan Africa.4 Since the burden of HIV/tuberculosis co-infection is very high in many low-income and middle-income countries,5 many of the patients who enter ART programmes in these settings have a current diagnosis of tuberculosis, or later develop tuberculosis following initiation of ART. For example, one South African study reported that 238 (25%) of 944 patients attending a community-based ART programme were receiving tuberculosis treatment at ART initiation and in the first year of ART the incidence of tuberculosis was 13·4 cases per 100 person-years (95% CI 10·4–16·9).6 Up to one-third of patients with HIV/tuberculosis co-infection who begin ART in such settings could be at risk of developing tuberculosis-associated IRIS (also known as TB-IRIS),3 and this condition is emerging as an important clinical challenge in resource-limited settings.[7–10]

Since there is no diagnostic test for IRIS, confirmation of the disease relies heavily upon case definitions incorporating clinical and laboratory data. However, clinical management and research on IRIS are hindered by the lack of consensus case definitions and definitions that are specific to particular opportunistic infections. To address this shortcoming, an international meeting of researchers working in this field was convened in Kampala, Uganda, in November, 2006, and the International Network for the Study of HIV-associated IRIS (INSHI) was formed. The specific aim of the meeting was to develop consensus case definitions for tuberculosis-associated IRIS that are appropriate for low-income settings where laboratory capacity is often limited, and that can be used by researchers working in dierent settings to permit comparability of results. We present these consensus case definitions in this paper.

Participants and consensus methods

The need for a public-health definition for tuberculosis-associated IRIS was first proposed at the WHO consultation on tuberculosis and HIV research priorities in resource-limited settings in February, 2005.11 The organisers of the meeting in Kampala contacted individuals involved in research related to tuberculosis-associated IRIS, particularly those working in resource-limited settings or collaborating with researchers in these settings. Contacting these individuals was dependent on whether they had published or presented data about tuberculosis-associated IRIS at international conferences, whether they were involved in ongoing research projects about the disease, or whether they had clinical experience of the disease. 97 researchers from 16 countries on six continents attended the meeting. Among the delegates were microbiologists, immunologists, clinicians, epidemiologists, clinical trialists, public-health specialists, and representatives from WHO.

At the meeting a subgroup was assembled to develop the case definitions. Two participants presented published IRIS case definitions (panel 1)[2,7,12–14] as well as eight dierent tuberculosis-associated IRIS case definitions currently being used by researchers in ongoing cohort and intervention studies. The common features among these case definitions were highlighted, and their practical use in resource-limited settings was discussed. Tuberculosis-associated IRIS case definitions were agreed and taken back to a plenary session for further discussion and consensus building. Thereafter,

Panel 1

Existing case definitions for IRIS and tuberculosis-associated IRIS that have been most widely used

General IRIS case definition 1 (French et al, 2004)2

Diagnosis requires two major criteria (A+B) or major criterion (A) plus two minor criteria to be fulfilled:

Major criteria

(A) Atypical presentation of opportunistic infections or tumours in patients responding to ART

- Localised disease
- Exaggerated inflammatory reaction
- Atypical inflammatory response in affected tissues
- Progressive organ dysfunction or enlargement of pre-existing lesions after definite clinical improvement with pathogen-specific therapy before the initiation of ART and exclusion of treatment toxicity and new alternative diagnoses

(B) Decrease in plasma HIV RNA concentration by more than 1 $\log_{10}$ copies per mL

Minor criteria

- Increase in blood CD4 T-cell count after starting ART
- Increase in an immune response specific to the relevant pathogen—eg, delayed-type hypersensitivity skin test response to mycobacterial antigens
- Spontaneous resolution of disease without specific antimicrobial therapy or tumour chemotherapy with continuation of ART

General IRIS case definition 2 (Shelburne et al, 2006)13

Criteria for IRIS diagnosis include:

- HIV-infected patient
- Receiving effective ART as evidenced by a decrease in HIV-1 RNA concentration from baseline or an increase in CD4+ T cells from baseline (may lag behind HIV-1 RNA decrease)
- Clinical symptoms consistent with inflammatory process
- Clinical course not consistent with expected course of previously diagnosed opportunistic infection, expected course of newly diagnosed opportunistic infection, or drug toxicity

Case definition specific for tuberculosis-associated IRIS (Colebunders et al, 2006)7

For patients receiving treatment for tuberculosis and starting ART:

Suspected tuberculosis-associated IRIS case

Cases must meet the following three criteria:

- An initial clinical response to tuberculosis treatment, based on a combination of some of the following factors: cessation of fever, relief of pulmonary symptoms, decrease in lymph node size, termination of signs of meningeal irritation (depending on presenting symptoms)
- New persistent fevers without another identifiable cause and/or one or more of the following: worsening or emergence of dyspnoea, stridor, an increase in lymph node size, development of abscesses, development of abdominal pain with ultrasound evidence of abdominal adenopathies, unexplained CNS symptoms
- Adequate adherence to ART and tuberculosis treatment

Confirmed tuberculosis-associated IRIS case

Cases must meet the following three criteria:

- Radiological examinations showing worsening or emergence of intrathoracic lymphadenopathy, pulmonary infiltrates, pleural effusions, abdominal lymph nodes, hepatosplenomegaly
- A good virological response and/or increase in CD4+ lymphocyte count, and/or conversion of tuberculin skin test from negative to positive, and/or adequate adherence to ART and tuberculosis treatment
- A clear exclusion of other conditions that could explain the clinical manifestations of the patient, such as tuberculosis treatment failure or other concomitant infections, tumours, or allergic reactions

ART=antiretroviral therapy. IRIS=immune reconstitution inflammatory syndrome.

a writing committee of 17 members was appointed to finalise the consensus case definitions.

Changes to existing case definitions

General case definitions for IRIS have previously been published (panel 1).[2,12–14] These case definitions include the following criteria: confirmed HIV diagnosis, temporal association with initiation of ART, demonstration of response to ART (ie, plasma viral load reduction, blood CD4 cell count increase, or another marker of immune recovery such as conversion of tuberculin skin test from negative to positive for mycobacterial IRIS), clinical deterioration with an inflammatory process, and exclusion of other causes that could explain deterioration (such as antimicrobial drug resistance, drug hypersensitivity reaction, or another opportunistic infection). However, since manifestations of IRIS are infection-specific, it has been recognised that particular definitions applicable to individual diseases such as tuberculosis would be useful.7 The case definitions presented in this manuscript focus specifically on the clinical manifestations of tuberculosis-associated IRIS.

Case definitions should be readily applicable in resource-limited settings where the vast majority of patients requiring ART live and yet where facilities for diagnosis and management of the complications of ART are least well developed. In this respect, the requirement within existing definitions for documentation of changes in CD4 cell count and plasma viral load is not achievable in these settings. Viral load testing has limited

availability and is very costly. In the South African public sector a viral load test costs US $39, more than the cost of 1 month's supply of first-line ART. Even where CD4 and viral load testing are available (such as in South Africa), use of these tests under programmatic conditions is usually permitted for monitoring of ART at 6-monthly intervals only and not for individual patient diagnostic work-up.

We believe that omission of these laboratory parameters would not substantially compromise case definitions for tuberculosis-associated IRIS. First, within the initial months of ART—when most cases of tuberculosis-associated IRIS arise—most ART-naive patients adhering to treatment have substantial viral load reductions;[15–17] thus, inclusion of viral load changes in definitions is largely redundant in the context of a patient who adheres to therapy. Second, tuberculosis-associated IRIS frequently develops shortly after initiation of ART and before any measurable increase in peripheral blood CD4 cell count. In a series of 51 patients presenting with non-tuberculous mycobacterial IRIS, six (12%) of 51 IRIS events occurred without a substantial increase in CD4 cell count (four patients had a CD4 increase from baseline to time of IRIS diagnosis of less than 25 cells per μL and in two patients the CD4 cell count had actually fallen at the time of presentation).18 The number of CD4 T cells measured in peripheral blood does not necessarily reflect function nor how many cells are actually present at the site of an opportunistic infection. Moreover, it is very likely that CD4 T cells are not the only cellular mediators of IRIS.19,20 For these reasons we, like others,12 propose that a rise in peripheral blood CD4 cell count should not be a necessary marker for the diagnosis of tuberculosis-associated IRIS.

A further important modification to existing definitions is the inclusion of a timeframe of the first 3 months of ART. Such a timeframe is not present in the widely used case definitions to date (panel 1). Onset of the clinical manifestations of tuberculosis-associated IRIS should occur within this timeframe for a diagnosis of tuberculosis-associated IRIS to be made, since this represents the period when rapid immune recovery usually occurs.3,21

Categories of tuberculosis-associated 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 (here termed 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 reaction (here termed unmasking tuberculosis-associated IRIS).

Paradoxical tuberculosis-associated IRIS

In paradoxical tuberculosis-associated IRIS, patients have been diagnosed with active tuberculosis before initiation of ART, and have typically been responding to antituberculosis treatment. Following initiation of ART, IRIS presents as the development of recurrent, new, or worsening symptoms or signs of tuberculosis, such as fever, return of cough, or lymph node enlargement, or recurrent, new, or deteriorating radiological manifestations (figure 1). These symptoms typically occur within the first few weeks and up to 3 months after ART is initiated, restarted, or changed because of treatment failure.

Reports of the frequency of paradoxical tuberculosis-associated IRIS using a variety of existing case definitions range from 8% to 43% (table).[8–10,21–28] Paradoxical tuberculosis-associated IRIS has been linked with large expansions of purified protein derivative-specific T cells in peripheral blood and increased pro-inflammatory cytokine levels.29 Risk factors for the disease are shown in table 1 and include more advanced HIV disease with lower CD4 cell count, disseminated and extrapulmonary tuberculosis, a shorter delay between the start

of tuberculosis treatment and initiation of ART, and a more vigorous immunological and virological response to ART. Most cases of paradoxical tuberculosis-associated IRIS are self-limiting. The median duration of symptoms reported in the literature is 2 months,26,28 but this ranges from mild cases where symptoms resolve after a few days to isolated prolonged cases that have still been symptomatic after more than a year (figure 1).28 Mortality from tuberculosis-associated IRIS has been reported infrequently in the literature, 3,9,10,26 but morbidity and the need for hospital admission and therapeutic procedures can be substantial.26 Rates of morbidity and mortality attributable to paradoxical tuberculosis-associated IRIS may be higher in resource-limited settings where diagnostic and treatment options are restricted. Neurological tuberculosis-associated IRIS in particular can be associated with poor outcome.

Tuberculosis paradoxical reactions, such as enlargement of lymph nodes or cerebral tuberculomas, can also occur in HIV-uninfected individuals and HIV-infected individuals who are receiving appropriate tuberculosis treatment but who are not receiving ART;[30–32] however, the frequency of paradoxical reactions is much lower in these groups compared with patients receiving ART.22,23 In one study, paradoxical reactions following tuberculosis treatment occurred in one (2%) of 55 HIV-seronegative patients, two (7%) of 28 HIV-infected patients not on ART, and 12 (36%) of 33 HIV-infected patients on tuberculosis treatment and ART.22 The timing of the paradoxical reaction in the latter group was more closely related to the initiation of ART than it was to the initiation

Panel 2

Case definition for paradoxical tuberculosis-associated IRIS

There are three components to this case definition:

(A) Antecedent requirements

Both of the two following requirements must be met:

- Diagnosis of tuberculosis: the tuberculosis diagnosis was made before starting ART and this should fulfil WHO criteria for diagnosis of smear-positive pulmonary tuberculosis, smear-negative pulmonary tuberculosis, or extrapulmonary tuberculosis44
- Initial response to tuberculosis treatment: the patient's condition should have stabilised or improved on appropriate tuberculosis treatment before ART initiation—eg, cessation of night sweats, fevers, cough, weight loss. (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 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—eg, tuberculous arthritis
- New or worsening radiological features of tuberculosis (found by chest radiography, abdominal ultrasonography, CT, or MRI)

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- New or worsening CNS tuberculosis (meningitis or focal neurological deficit—eg, 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, dyspnoea, 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 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

ART=antiretroviral therapy. IRIS=immune reconstitution inflammatory syndrome. *It might be difficult or impossible in resource-poor settings to confirm tuberculosis 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 tuberculosis-associated IRIS”. In these probable cases, should resolution of clinical or radiological findings of the suspected IRIS episode occur without a change in tuberculosis treatment or ART having been made, they could then be reclassified as ”paradoxical tuberculosis-associated IRIS” cases.

of tuberculosis treatment. Thus, the greatly increased frequency of paradoxical reactions in patients receiving ART suggests that ART-related immunological changes have an important role in their aetiology. Additionally, our clinical experience is that paradoxical tuberculosis-associated IRIS is more severe and more frequently a multisystemic condition in ART patients than paradoxical reactions in patients not receiving ART.

ART-associated tuberculosis and unmasking tuberculosis-associated IRIS

Compared with paradoxical tuberculosis-associated IRIS, there is much less clarity surrounding the second major category of tuberculosis-associated-IRIS. High rates of tuberculosis have been diagnosed during ART, especially in the initial months of treatment in ART programmes in resource-limited settings.[6,33–36] The mechanisms underlying the presentation of tuberculosis after the initiation of ART are likely to be heterogeneous.37 Since ART-induced immune recovery is a time-dependent process and some patients initially fail to show an increased circulating CD4 T-cell count,38,39 a proportion of cases might present as a result of persisting immunodeficiency. Diagnoses of active tuberculosis before ART initiation might be missed because of the inherent insensitivity of tuberculosis diagnostics in patients with advanced immunodeficiency and only confirmed later during ART. Other patients might have active subclinical disease at the time of ART initiation and presentation of symptomatic disease might result from ART-induced restoration of an immune response against *Mycobacterium tuberculosis* antigens that causes inflammation.

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Some patients with a missed tuberculosis diagnosis or active subclinical tuberculosis at the time of ART initiation may later present with exuberant inflammatory clinical features that are consistent with a diagnosis of unmasking tuberculosis-associated IRIS (figure 2).

Paradoxical reactions in patients started on tuberculosis treatment while receiving ART have also been described,26,40 and one study reported that paradoxical reactions are more frequent in patients who are diagnosed with tuberculosis in the first 3 months of ART than in patients who start ART after tuberculosis treatment (eight [62%] of 13 patients *vs* nine [30%] of 30 patients, respectively, p=0·05).40 This finding suggests that ART-related immunological changes have a role in the development of paradoxical reactions in patients who present with tuberculosis while receiving ART and that these reactions are a form of tuberculosis-associated IRIS.

Only a few cases of unmasking tuberculosis-associated IRIS have been described in the literature to date.[40–43] In the absence of a diagnostic test, it is currently difficult to dierentiate the varied mechanisms underlying most cases of tuberculosis that present during early ART, especially in resource-limited settings where rates of infection are high. We therefore propose that, as elsewhere,37 the term ART-associated tuberculosis is used

Panel 3

Case definition for ART-associated tuberculosis and provisional case definition for unmasking tuberculosis-associated IRIS

ART-associated tuberculosis

We propose that ART-associated tuberculosis (all cases of tuberculosis that are diagnosed during ART) should be defined as follows:

- Patient is not receiving treatment for tuberculosis when ART is initiated
- Active tuberculosis is diagnosed after initiation of ART
- The diagnosis of tuberculosis should fulfil WHO criteria for smear-positive pulmonary tuberculosis, smear-negative pulmonary tuberculosis, or extrapulmonary tuberculosis44

Unmasking tuberculosis-associated IRIS (provisional)

We propose that the following could suggest a diagnosis of unmasking tuberculosis-associated IRIS:

- Patient is not receiving treatment for tuberculosis when ART is initiated and then presents with active tuberculosis within 3 months of starting ART

AND one of the following criteria must be met:

- Heightened intensity of clinical manifestations, particularly if there is evidence of a marked inflammatory component to the presentation. Examples include tuberculosis lymphadenitis or tuberculosis abscesses with prominent acute inflammatory features, presentation with pulmonary tuberculosis that is complicated by respiratory failure due to adult respiratory distress syndrome, and those who present with a marked systemic inflammatory syndrome related to tuberculosis. See example in figure 2
- Once established on tuberculosis treatment, a clinical course that is complicated by a paradoxical reaction

ART=antiretroviral therapy. IRIS=immune reconstitution inflammatory syndrome. Researchers in the field are encouraged not to regard all patients with ART-associated tuberculosis as having tuberculosis-associated IRIS, but only those that fit this provisional unmasking tuberculosis-associated-IRIS case definition. We suggest that the clinical manifestations of all patients developing ART-associated tuberculosis should be well characterised and reported in studies, which will assist with refinement of this case definition in the future. Studies of the immunological processes underlying the presentation of these cases are also likely to assist with refining this case definition.

to refer to all patients who present with active tuberculosis while receiving ART (figure 3). We also suggest a provisional case definition for unmasking tuberculosis-associated IRIS and clinical scenarios where the diagnosis could be considered.

Further research into the clinical characteristics and immunological mechanisms underlying cases of ART-associated tuberculosis will permit a more refined case definition for unmasking tuberculosis-associated IRIS in the future. However, in view of the heterogeneity in the natural history and clinical manifestations of tuberculosis it is unlikely that a clinical case definition that robustly separates patients with unmasking tuberculosis-associated IRIS from others with ART-associated tuberculosis will be derived.37

Case definitions

With the rationale described above, we have developed case definitions for “paradoxical tuberculosis-associated IRIS” (panel 2), “ART-associated tuberculosis” (panel 3), and “unmasking tuberculosis-associated-IRIS” (panel 3). The case definitions are presented schematically in figure 3. These case definitions have been designed for use in resource-limited settings and are consensus case definitions that need validation in clinical practice.

Search strategy and selection criteria

Data for this Personal View were obtained by searching Medline for articles published from 1990 to 2008. Search terms included “immune reconstitution”, “immune restoration”, “immune recovery”, “IRIS”, “antiretroviral”, “tuberculosis”, and “paradoxical reaction”. Only English language papers were reviewed. Additionally, unpublished data and tuberculosis-associated IRIS case definitions presented by researchers at the INSHI meeting were used.

Conclusions

The use of standardised case definitions in different populations will help to provide greater insight into the incidence, clinical manifestations, risk factors, and impact of tuberculosis-associated IRIS, ultimately leading to better prevention and management strategies for this condition. Further clinical and immunological research on patients with ART-associated tuberculosis is needed to better dierentiate the subset of cases that have unmasking tuberculosis-associated IRIS and to further refine this case definition. It is hoped that open research networks such as INSHI will provide opportunities for researchers to engage in collaborative research into tuberculosis-associated IRIS using these case definitions.

Acknowledgments

This manuscript arose from a meeting of the International Network for the Study of HIV-associated IRIS (INSHI) hosted by the Infectious Diseases Institute, Makerere University, Kampala, Uganda. This meeting was funded by the European and Developing Countries Clinical Trials Partnership Programme, the Belgian General Development

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Corporation, the Research Foundation-Flanders, and Tibotec. Graeme Meintjes, Stephen D Lawn, and Robert J Wilkinson are funded by the Wellcome Trust, UK. Martyn French is supported by the National Health and Medical Research Council, Australia. We thank Dominique J Pepper for assistance with preparing the illustrative case in figure 1 and Charles Steinberg for providing the radiographs in figure 2.

The following participants attended the INSHI meeting: Francis Adatu (National TB Control Programme, Kampala, Uganda), Rebecca Adlington (Médecins Sans Frontières, Bukavu, Democratic Republic of the Congo), Barbara Amuron (MRC/Uganda Virus Research Institute, Entebbe, Uganda), Per Bjorkman (Lund University, Malmoe, Sweden), Paul Bohjanen (University of Minnesota, Minneapolis, MN, USA), David Boulware (University of Minnesota, Minneapolis, MN, USA), Steven Callens (Catholic University Leuven, Leuven, Belgium), Mariah Carroll (University of Minnesota, Minneapolis, MN, USA), Barbara Castelnuovo (Infectious Disease Institute, Kampala, Uganda), Robert Colebunders (Institute Tropical Medicine and University of Antwerp, Antwerp, Belgium), Caroline De Schacht (Elizabeth Glaser Pediatric AIDS Foundation, Maputo, Mozambique), Aggrey Dhabangi (Paediatric Infectious Disease Institute, Kampala, Uganda), Philippa Easterbrook (Kings College, London, UK), Alison Elliot (MRC/Uganda Virus Research 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(Makerere University, Kampala, Uganda), Francis Okidi (Gulu, Uganda), Martin Okot Nwang (Mulago Hospital, Kampala, Uganda), Alphonse Okwera (Mulago Hospital, Kampala, Uganda), Pascale Ondoa (Institute Tropical Medicine, Antwerp, Belgium), Eric Ouattara (Programme PAC-CI, Abidjan, Côte d'Ivoire), Nadine Pakker (Project Interact, Kampala, Uganda), Rosalind Parkes (MRC/Uganda Virus Research Institute, Masaka, Uganda), Dylan Pillai (University of California, San Francisco, CA, USA), Molebogeng Rangaka (University of Cape Town, Cape Town, South Africa), Peter Reiss (Academic Medical Center, Amsterdam, Netherlands), Steven Reynolds (SAIC Frederick, MD, USA), Fabio Scano (WHO, Geneva, Switzerland), Kinda Schepers (Free University Brussels, Brussels, Belgium), Maarten Schim van der Loe (Academic Medical Center, Amsterdam, Netherlands), Walter Schlech (Dalhousie University, Halifax, Canada), Paul Seguya (Kampala, Uganda), Semitala Fred (Mulago Hospital, Kampala, Uganda), Ibrahim Sendagire 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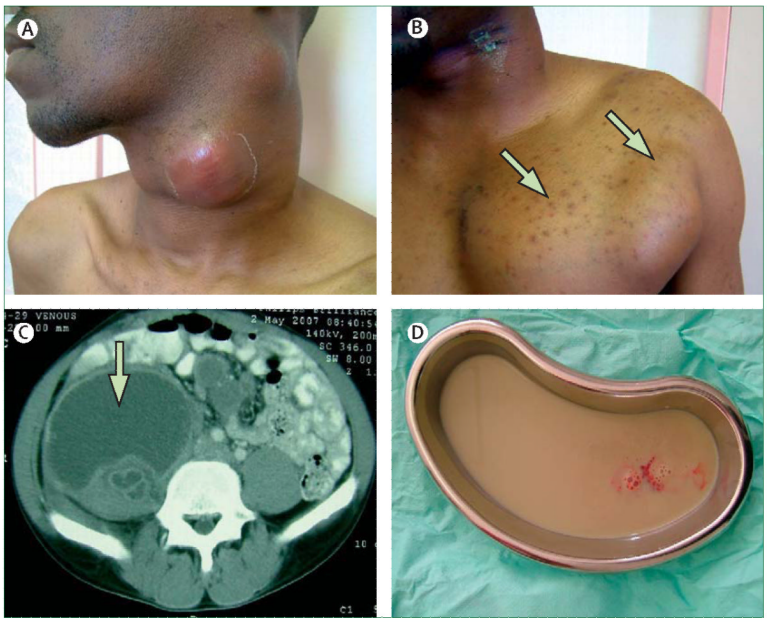

Figure 1. Illustrative case of paradoxical tuberculosis-associated IRIS

A 36-year-old HIV-infected man was diagnosed with culture-positive pulmonary tuberculosis (sensitive to rifampicin and isoniazid) without evidence of extrapulmonary involvement. His CD4 count was 39 cells per μL and HIV-1 viral load 1 300 000 copies per mL. He commenced antiretroviral therapy (ART; stavudine, lamivudine, and efavirenz) 7 weeks after initiating antituberculous therapy. 1 week later he presented with a recurrence of tuberculosis symptoms and cervical node enlargement. Paradoxical tuberculosis-associated IRIS was diagnosed. Over the next 18 months he presented with several tuberculosis-associated IRIS manifestations that sequentially emerged, despite corticosteroid therapy, then resolved. Photographs show development of massive cervical lymphadenitis (A), a chest wall cold abscess (B, arrows), and a massive right psoas abscess shown here on CT scan (C, arrow) from which over 2 L of pus was aspirated (D). Repeated mycobacterial cultures of aspirates from these collections have been negative. After 6 months on ART his CD4 count was 181 cells per μL and viral load undetectable. After 12 months his CD4 count was 448 cells per μL and viral load 35 copies per mL. This was an unusually prolonged course for paradoxical tuberculosis-associated IRIS given that the median duration of symptoms is reported to be 2 months (see text).

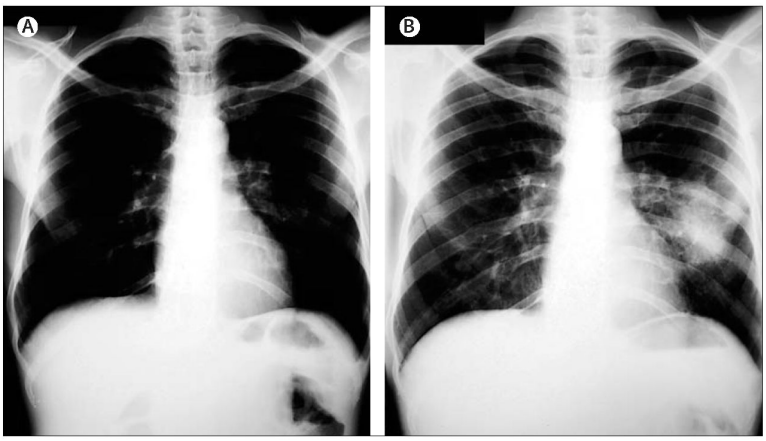

Figure 2. Illustrative case of unmasking tuberculosis-associated IRIS

A 48-year-old HIV-infected man with a CD4 count of 10 cells per μL presented with low-grade fevers, retrosternal chest pain, and a dry cough. Examination was non-contributory. He could not produce sputum and his chest radiograph showed no features of active tuberculosis (A). No other investigations for tuberculosis were available in this resource-limited setting (Uganda). Antiretroviral therapy (ART) was started (zidovudine, lamivudine, and efavirenz). 10 days later he returned acutely unwell with a productive cough. His temperature was 38·7°C and he was in respiratory distress. Chest radiograph now showed left mid-zone consolidation (B) and his sputum was positive for acid-fast bacilli. The unusual rapidity and clinical severity of his tuberculosis presentation was attributed to unmasking tuberculosis-associated IRIS. He responded well to continued ART and tuberculosis treatment.

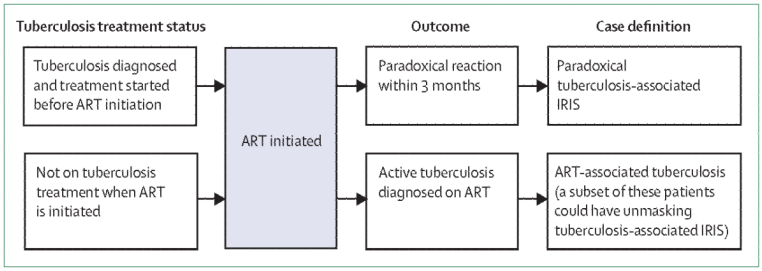

Figure 3. Schematic representation showing the different forms of tuberculosis-associated IRIS and ART-associated tuberculosis

ART=antiretroviral therapy.

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Table

Paradoxical tuberculosis-associated IRIS: cohort studies reported in the literature*

	Country	Number of patients on tuberculosis treatment starting ART	Number of patients with paradoxical tuberculosis-associated IRIS	Interval from initation of ART to IRIS presentation	Risk factors for tuberculosis-associated IRIS
Narita et al (1998)22	USA	33	12 (36%)	Mean 15 days (SD 11 days)	Purified protein derivative conversion
Breen et al (2004)23	UK	28	8 (29%)	Median 11 days (range 8–18 days)	Starting ART within 6 weeks of tuberculosis diagnosis
Breton et al (2004)24	France	37	16 (43%)	Median 12 days (range 2–114 days)	Greater increase in CD4 percentage and CD4/CD8 ratio; disseminated tuberculosis
Kumarasamy et al (2004)8	India	144	11 (8%)	Median 42 days (range 10–89 days)	..
Shelburne et al (2005)†21	USA	86	26 (30%)	Median 46 days (range 3–658 days)	Shorter interval to starting ART; more rapid initial fall in viral load
Michailidis et al (2005)‡25	UK	28	9 (32%)	Median 0·6 months (IQR 0·1–9·1 months)	Lower baseline CD4 cell count; disseminated tuberculosis; greater CD4 rise on ART
Manosuthi et al (2006)9	Thailand	167	21 (13%)	Median 32 days (IQR 14–115 days)	Extrapulmonary tuberculosis
Lawn et al (2007)10	South Africa	160	19 (12%)	Median 2 weeks (IQR 1·5–3·5 weeks)	Lower baseline CD4 cell count; shorter interval to starting ART
Burman et al (2007)26	USA	109	19 (17%)	Median 34 days (IQR 8–97 days)	Black ethnic origin; shorter interval to starting ART; extrapulmonary tuberculosis

..=not reported. ART=antiretroviral therapy. IRIS=immune reconstitution infl ammatory syndrome.

*Only studies where more than eight patients with paradoxical tuberculosisassociated IRIS were reported are included. This table is an updated version of a previously published table. 27 Studies are presented in chronological order.

†The authors reported 57 cases of tuberculosis, *Mycobacterium avium* complex, and cryptococcal IRIS (26 of 57 were tuberculosis-associated IRIS). Five of these 57 patients started ART before the opportunistic infection was diagnosed, and were thus not paradoxical IRIS cases. The data shown regarding risk factors and median interval relate to all 57 patients.

‡14 tuberculosis-associated IRIS cases were reported. Nine of these were paradoxical tuberculosis-associated IRIS cases. Data shown regarding risk factors relate to all 14 cases.