Personal View

Tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS): case definitions for use in resource-limited settings

Running head: TB-IRIS Case Definitions

Meintjes Graeme¹ MRCP, FCP(SA), Lawn Stephen D²,³ MD, Scano Fabio⁴ MD, Maartens Gary⁵ FCP(SA), French Martyn A⁶ MD FRACP, Worodria William⁷ MD, Elliott Julian H⁸ MD, Murdoch David⁹ MD, Wilkinson Robert J¹⁰,¹¹ MRCP PhD, Seyler Cathérine¹² MD PHD, John Laurence¹³ MRCP, Schim van der Loeff Maarten¹⁴ MD, PhD, Reiss Peter¹⁴ MD, PHD, Lynen Lut¹⁵ MD, Janoff Edward N¹⁶ MD, Gilks Charles¹⁷ DPhil FRCP, Colebunders Robert¹⁵,¹⁸* MD, PHD

For the International Network for the Study of HIV-associated IRIS (INSHI)

¹ Institute of Infectious Diseases and Molecular Medicine and Department of Medicine, University of Cape Town, South Africa

² Desmond Tutu HIV Centre, Institute for Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

³ Clinical Research Unit, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK

⁴ HTM/STB/THD, World Health Organization, Geneva, Switzerland

⁵ Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, South Africa
6 Department of Clinical Immunology, Royal Perth Hospital and School of Pathology and Laboratory Medicine, University of Western Australia, Perth, Australia.

7 Infectious Diseases Institute, Makerere University, Uganda

8 National Centre in HIV Epidemiology and Clinical Research, Australia

9 Duke University Medical Center, Durham, North Carolina and University of North Carolina at Chapel Hill, US

10 National Institute for Medical Research, Mill Hill, London, NW7 1AA, UK

11 Wellcome Trust Center for Research in Clinical Tropical Medicine, Division of Medicine, Imperial College London, W2 1PG, UK.

12 Institut de Santé Publique, d’Épidémiologie et de Développement (ISPED), Bordeaux 2 University, Bordeaux, France

13 Chelsea and Westminster Hospital, London, England

14 Center for Poverty-related Communicable Diseases, Academic Medical Centre, Amsterdam, The Netherlands

15 Institute of Tropical Medicine, Antwerp, Belgium

16 Colorado Center for AIDS Research, University of Colorado, Colorado, US

17 HIV Department, World Health Organization, Geneva, Switzerland

18 University of Antwerp, Antwerp, Belgium
*Corresponding author

Robert Colebunders
Institute of Tropical Medicine
Nationalestraat 155
Antwerp
Belgium

bcoleb@itg.be

Word Count:
Abstract = 155; Text = 2956; Tables = 3; Figures = 4; References = 42

Key words:
HIV/AIDS; tuberculosis; antiretroviral therapy; immune reconstitution inflammatory syndrome; IRIS; immune reconstitution disease.
Abstract

The immune reconstitution inflammatory syndrome (IRIS) has emerged as an important early complication of antiretroviral therapy in resource-limited settings, especially in patients with tuberculosis (TB). However, there are no consensus case definitions for IRIS or TB-associated IRIS (TB-IRIS). Moreover, case definitions that have been previously proposed are not readily applicable in resource-limited settings where laboratory resources are often limited. As a result, existing studies on TB-IRIS have employed a variety of non-standardised general case definitions. To rectify this, around 100 researchers (microbiologists, immunologists, clinicians, epidemiologists, clinical trialists, and public health specialists) from 16 countries met in Kampala, Uganda, in November 2006. In this meeting consensus case definitions for ‘paradoxical TB-IRIS’, ‘ART-associated TB’ and ‘unmasking TB-IRIS’ were derived that can be used not only in high-income but also in resource-limited settings. It is envisaged that these definitions may be used by clinicians and researchers in a variety of settings to promote standardisation and comparability of data.
Introduction

The immune reconstitution inflammatory syndrome or IRIS (elsewhere referred to as ‘immune reconstitution disease’, ‘immune reconstitution syndrome’ or ‘immune restoration disease’) is a widely recognised phenomenon that may complicate antiretroviral therapy (ART) 1, 2. It results from rapid restoration of pathogen-specific immune responses to opportunistic infections (OI), causing either the deterioration of a treated OI or the new presentation of previously subclinical OI. IRIS typically occurs during the initial months of ART and is recognised to be 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 a total of over 2 million people by December 2006 with an estimated 1 340 000 of these living in sub-Saharan Africa 4. Since the burden of TB/HIV co-infection is very high in many low and middle income countries 5, many patients enter ART programmes in these settings with a current diagnosis of TB or later develop TB following initiation of ART. For example, one South African study reported that 25% of patients were receiving TB treatment at ART initiation and a further 11% developed TB during the first year of ART 6. A substantial number of patients in such programmes are therefore at risk of developing TB-IRIS and this condition has emerged as an important clinical challenge in resource-limited settings 7-10.
There is no diagnostic test for IRIS and diagnoses therefore rely heavily upon case definitions incorporating clinical and laboratory data. However, both clinical management and research on IRIS are hindered by the lack of consensus case definitions and definitions that are specific to particular opportunistic infections. An international meeting of around 100 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 (Figure 1). A specific aim of the meeting was to develop consensus case definitions for TB-IRIS that are appropriate for resource limited settings (where laboratory capacity is often limited) and that could be used by researchers working in different settings to permit comparability of results. We present these consensus case definitions in this paper.

Participants and consensus method

The need for a public health definition for TB-IRIS was first conceptualized at the World Health Organisation (WHO) consultation on TB/HIV research priorities in resource limited settings in February 2005. The organizers of the meeting in Kampala contacted researchers involved in research related to TB-IRIS, particularly those working in resource limited settings or collaborating with researchers in these settings. Persons were contacted because they published or presented data about TB-IRIS at international conferences or because they were involved in ongoing research projects about TB-IRIS. Others were invited because of their clinical experience. Around 100 researchers from 16 countries on 6 continents attended the meeting. Among the delegates were
microbiologists, immunologists, clinicians, epidemiologists, clinical trialists, public health specialists and representatives from the WHO.

At the meeting a subgroup met to develop the case definitions. Two participants presented published IRIS case definitions\(^2,7,12-14\) as well as 8 different TB-IRIS case definitions being used by researchers in ongoing cohort and intervention studies (Table 1). The common features among these case definitions were highlighted. The issue of what was practical in resource limited settings was discussed. Consensus TB-IRIS case definitions were agreed then taken back to a plenary session for further discussion and consensus building. Thereafter a writing committee of 17 members was appointed to finalise the case definitions.

**Changes to existing case definitions**

General case definitions for IRIS have previously been published\(^2,12-14\). These case definitions include the following criteria: confirmed HIV diagnosis, temporal relationship with initiation of ART, demonstration of response to ART (plasma viral load [VL] reduction, blood CD4 cell count increase or another marker of immune recovery), clinical deterioration with an inflammatory process and exclusion of other aetiologies that could explain deterioration (such as antimicrobial drug resistance, drug hypersensitivity reaction or another opportunistic infection). However, since manifestations of IRIS are disease-specific, it has been recognised that specific definitions applicable to individual diseases such as TB would be useful\(^7\). Case definitions presented here focus specifically on the clinical manifestations of TB-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 VL is a major hindrance in these settings. VL testing is very limited in availability and costly. In the South African public sector a VL test costs US$ 39, more than the cost of one month’s supply of first line ART. Even where CD4 and VL testing are available (such as in South Africa), use of these tests under programmatic conditions is often proscribed for 6-monthly monitoring purposes only and not for individual patient diagnostic work-up.

It is important to emphasize, however, that we believe that omission of these laboratory parameters would not significantly compromise these definitions. The reason for this suggestion is firstly that the vast majority of ART-naïve patients adhering to treatment have substantial VL reductions within the initial months of ART when most cases of TB-IRIS present \(^{15-17}\); thus, inclusion of VL changes in definitions is largely redundant in the context of a patient adherent to therapy. Secondly, TB-IRIS not infrequently develops shortly after initiation of ART and prior to any measurable increase in peripheral blood CD4 cell count. In a series of 51 patients presenting with non-tuberculous mycobacterial IRIS, approximately 10% of IRIS events occurred without a substantial increase in CD4 count and in two patients the CD4 count had actually fallen at the time of presentation \(^{18}\). CD4 cell count numbers in peripheral blood do not necessarily reflect function nor
numbers 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. For these reasons we, like others\textsuperscript{12}, propose that a rise in peripheral blood CD4 cell count should not be a necessary condition for the diagnosis of TB-IRIS.

A further important modification to existing definitions is the inclusion of a time-frame of the first three months of ART. Onset of the clinical manifestations of TB-IRIS should occur within this time-frame for a diagnosis of TB-IRIS to be made since this is the period of most rapid immune recovery within which the vast majority of cases are concentrated\textsuperscript{3,19}.

**Categories of TB-IRIS**

TB-IRIS may present as one of two main syndromes: 1) a paradoxical reaction after the start of ART in patients receiving TB treatment (here termed ‘paradoxical TB-IRIS’) or 2) a new presentation of TB that is ‘unmasked’ in the weeks following initiation of ART that has an exaggerated inflammatory clinical presentation or is complicated by a paradoxical reaction (here termed ‘unmasking TB-IRIS’).

In the first of these two syndromes (‘paradoxical TB-IRIS’), patients have a diagnosis of active TB established prior to 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 TB, such as return of cough, fever or lymph node enlargement, or recurrent, new or deteriorating radiological
manifestations (Figure 2). This typically occurs within the first few weeks and up to 3 months after ART is initiated, re-started, or changed due to treatment failure.

Reports of the incidence of ‘paradoxical TB-IRIS’ using a variety of existing case definitions range between 8% and 43% \(8-10, 19-26\) (Table 2). ‘Paradoxical TB-IRIS’ has been associated with large expansions of purified protein derivative (PPD)-specific T-cells in peripheral blood as well as increased pro-inflammatory cytokine levels \(27\). Risk factors for TB-IRIS are shown in Table 2 and include more advanced HIV disease with lower CD4 cell count, disseminated and extrapulmonary TB, a shorter delay between the start of TB treatment and initiation of ART and a more vigorous immunological and virological response to ART. Most cases of ‘paradoxical TB-IRIS’ are self-limiting. The median duration of symptoms reported in the literature is 2 months \(23, 25\), but the duration is very variable ranging from mild cases where symptoms resolve after a few days to isolated prolonged cases that have still been symptomatic after more than a year \(23\) and Figure 2). Mortality due to TB-IRIS has infrequently been reported in the literature \(3, 9, 10, 25\), but morbidity and the need for hospitalisation and therapeutic procedures may be substantial \(25\). In resource limited settings where diagnostic and treatment options are restricted, the mortality and morbidity attributable to ‘paradoxical TB-IRIS’ may be greater. Neurological TB-IRIS in particular may be associated with poor outcome.

TB paradoxical reactions, such as enlargement of lymph nodes or cerebral tuberculomas, also occur in HIV-uninfected individuals and HIV-infected individuals who are receiving appropriate TB treatment but who are not receiving ART \(28-30\).
However, the frequency of paradoxical reactions is much greater with ART\textsuperscript{21, 24}. In one study, paradoxical reactions on TB treatment occurred in 2\% of HIV seronegative patients, 7\% of HIV-infected patients not on ART and 36\% of HIV-infected patients on TB treatment and ART\textsuperscript{21}. The timing of the paradoxical reaction in this latter group was more closely related to the initiation of ART than TB treatment. Thus, the greatly increased frequency of paradoxical reactions in patients receiving ART suggests that ART-related immunological changes play an important role in their aetiology. In addition, our clinical experience is that ‘paradoxical TB-IRIS’ is more severe and more frequently a multisystem condition than paradoxical reactions in patients not receiving ART.

There is less clarity surrounding the second major category of TB-IRIS (‘unmasking TB-IRIS’) than the first. High rates of TB have been described during ART, especially in the initial months of treatment in ART programmes in resource-limited settings\textsuperscript{6, 31-34}. The mechanisms underlying presentations of TB after initiating ART are likely to be heterogeneous\textsuperscript{35}. Since ART-induced immune recovery is a time-dependent process and some patients initially fail to experience an increased circulating CD4 T cell count\textsuperscript{36, 37}, a proportion of cases may present as a result of persisting immunodeficiency. Diagnoses of active TB prior to ART initiation may be missed due to the inherent insensitivity of TB diagnostics in this patient group and only be later diagnosed during ART. Other patients may have active sub-clinical disease at the time of ART initiation and presentation of symptomatic disease may result from ART-induced restoration of an immune response against MTB antigens that causes inflammation. Of patients in the latter two groups,
some have exuberant inflammatory clinical features that are consistent with a diagnosis of ‘unmasking TB-IRIS’ (Figure 3).

Paradoxical reactions in patients started on TB treatment while on ART are also described \(^{25,38}\) and one study reported that paradoxical reactions are more frequent in patients who are diagnosed with TB in the first 3 months of ART than patients who start ART after TB treatment (62 versus 30%, \(p = 0.05\)) \(^{38}\). This suggests that ART-related immunological changes play a role in the development of paradoxical reactions in this group of patients.

Few cases of ‘unmasking TB-IRIS’ have been described in the literature to date \(^{38-41}\). In the absence of a diagnostic test, it is currently difficult to differentiate the varied mechanisms underlying the majority of cases of TB that present during early ART, especially in resource-limited settings where rates of TB are extremely high. We therefore propose that, as elsewhere \(^{35}\), the term ‘ART-associated TB’ be used to refer to all patients who present with active TB while receiving ART (Figure 4). We also suggest a provisional case definition for ‘unmasking TB-IRIS’ and clinical scenarios where the diagnosis may be considered.

Further research into the clinical characteristics and immunological mechanisms underlying cases of ‘ART-associated TB’ may permit a more refined case definition for ‘unmasking TB-IRIS’ to be derived in the future. However, given the heterogeneity in the natural history and clinical manifestations of TB it is unlikely that a clinical case
definition that robustly separates patients with ‘unmasking TB-IRIS’ from others with ‘ART-associated TB’ will be derived 35.

**Case Definitions**

With the rationale described above, we have developed case definitions for ‘paradoxical TB-IRIS’, ‘ART-associated TB’ and ‘unmasking TB-IRIS’. These case definitions have been designed for use in resource-constrained settings and are consensus case definitions that need validation in clinical practice.

**Case Definition for ‘paradoxical TB-IRIS’ (summarised in Table 3)**

There are three components (A, B and C) to this case definition.

A) **Antecedant requirements**

Both of the two following requirements must be met:

1) **Diagnosis of TB**: The TB diagnosis was made before starting ART and this should fulfil World Health Organization (WHO) criteria for diagnosis of smear positive pulmonary TB (PTB), smear negative PTB or extrapulmonary TB 42.

2) **Initial response to TB treatment**: The patient’s condition should have stabilised or improved on appropriate TB treatment prior to ART initiation e.g. cessation of night sweats, fevers, cough, weight loss. (Note: this does not apply to patients starting ART 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 three months of ART initiation, re-initiation, or regimen change due to treatment failure. Of the following, at least 1 major criterion or 2 minor clinical criteria are required:

**Major criteria**

1) New or enlarging lymph nodes, cold abscesses or other focal tissue involvement (e.g. tuberculous arthritis)

2) New or worsening radiological features of TB (using chest radiography, abdominal ultrasonography, computerised tomography [CT] or magnetic resonance imaging [MRI]).

3) New or worsening central nervous system TB (meningitis or focal neurological deficit e.g. due to tuberculoma)

4) New or worsening serositis (pleural effusion, ascites or pericardial effusion)

**Minor criteria**

1) New or worsening constitutional symptoms such as fever, night sweats or weight loss.
2) New or worsening respiratory symptoms such as cough, dyspnoea or stridor.
3) New or worsening abdominal pain accompanied by peritonitis or hepatomegaly or splenomegaly or abdominal adenopathy.

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

1) Failure of TB treatment due to TB drug resistance
2) Poor adherence to TB treatment
3) 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).
4) 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 ART having been made they could then be reclassified as ‘paradoxical TB-IRIS’ cases.
**Case definition for ‘ART-associated TB’**

We propose that ‘ART-associated TB’ (all cases of TB that are diagnosed during ART) should be defined as follows.

1) Patient is not receiving treatment for TB when ART is initiated.
2) Active TB is diagnosed after initiation of ART.
3) The diagnosis of TB should fulfil WHO criteria for smear positive PTB, smear negative PTB or extrapulmonary TB 42.

**Case definition for ‘unmasking TB-IRIS’**

A sub-set of ‘ART-associated TB’ cases may be due to TB-IRIS. There are few reports in the literature upon which to base a case definition for this sub-set. Nonetheless we considered it necessary to propose a provisional case definition for this entity to assist researchers in collecting clinical and immunological data in order that a more refined case definition could be developed in the future. We propose that the following features may suggest a diagnosis of ‘unmasking TB-IRIS’:

1) Patient is not receiving treatment for TB when ART is initiated and then presents with active TB within 3 months of starting ART

AND

2) One of:

   a) 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 [ARDS] and those who present with a marked systemic inflammatory syndrome related to TB. See Figure 3.

b) Once established on TB treatment, a clinical course that is complicated by a paradoxical reaction

Researchers in the field are encouraged not to regard all patients with ‘ART-associated TB’ as having TB-IRIS, but only those that fit this provisional ‘unmasking TB-IRIS’ case definition. We suggest that the clinical manifestations of all patients developing ‘ART-associated TB’ should be well characterised and reported in studies. This 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.

**Conclusions**

Consensus case definitions for ‘paradoxical TB-IRIS’, ‘ART-associated TB’ and ‘unmasking TB-IRIS’ were established and these are readily applicable in resource-limited settings. Use of standardized case definitions in different populations may help to provide greater insight into the incidence, clinical manifestations, risk factors, and impact of TB-IRIS, ultimately leading to better prevention and management strategies for this
condition. Further clinical and immunological research on patients with ‘ART-associated TB’ is needed to better differentiate the sub-set of cases that have ‘unmasking TB-IRIS’ and 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 TB-IRIS using these case definitions.
Acknowledgements

This manuscript arose from a meeting of the International Network for the Study of HIV-associated IRIS (INSHI) that was generously 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 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. The authors have no conflicts of interest to declare.

Full List of Participants

Table 1: Search strategy

Data for this paper were obtained by searching Medline without time restrictions. Search terms included “immune reconstitution”, “immune restoration”, “immune recovery”, “IRIS”, “antiretroviral” and “tuberculosis” and “paradoxical reaction”. Only English language papers were reviewed. In addition, unpublished data and TB-IRIS case definitions presented by researchers at the meeting were used.
### Table 2: Paradoxical TB-IRIS: cohort studies reported in the literature

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Incidence of TB-IRIS</th>
<th>Median/mean interval from ART to IRIS (in days)</th>
<th>Significant associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narita [21]</td>
<td>United States</td>
<td>36%</td>
<td>15</td>
<td>PPD conversion</td>
</tr>
<tr>
<td>Olalla [23]</td>
<td>Spain</td>
<td>27%</td>
<td>18</td>
<td>Greater decrease in VL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower CD4 count at 6 months.</td>
</tr>
<tr>
<td>Breen [24]</td>
<td>United Kingdom</td>
<td>29%</td>
<td>11</td>
<td>Starting ART within 6 weeks of TB diagnosis</td>
</tr>
<tr>
<td>Breton [20]</td>
<td>France</td>
<td>43%</td>
<td>12</td>
<td>Greater increase in CD4 % and CD4/CD8 ratio</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Disseminated TB</td>
</tr>
<tr>
<td>Kumarasamy [8]</td>
<td>India</td>
<td>8%</td>
<td>42</td>
<td>NR</td>
</tr>
<tr>
<td>Shelburne [19]</td>
<td>United States</td>
<td>30%</td>
<td>46</td>
<td>Shorter interval to starting ART</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>More rapid initial fall in VL</td>
</tr>
<tr>
<td>Michailidis [22]</td>
<td>United Kingdom</td>
<td>26%</td>
<td>15</td>
<td>Lower baseline CD4 count</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Disseminated TB</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Greater CD4 rise on ART</td>
</tr>
<tr>
<td>Manosuthi [9]</td>
<td>Thailand</td>
<td>13%</td>
<td>32</td>
<td>Extrapulmonary TB</td>
</tr>
<tr>
<td>Lawn [10]</td>
<td>South Africa</td>
<td>12%</td>
<td>14</td>
<td>Lower baseline CD4 count</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Shorter interval to starting ART</td>
</tr>
<tr>
<td>Burman [25]</td>
<td>United States</td>
<td>15%</td>
<td>34</td>
<td>Black race</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Shorter interval to starting ART</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Extra-pulmonary TB</td>
</tr>
</tbody>
</table>

Abbreviations: NR = not reported; TB = tuberculosis; VL = viral load; PPD = purified protein derivative

1 Only those studies where > 8 patients with TB-IRIS have been reported are included. Studies are in chronological order. This table is an updated version of a previously published table [26].

2 In this study, 8 cases of the 9 were associated with TB, the other was associated with *Mycobacterium avium* complex (MAC). Data shown are for all 9.

3 Breen reported 14 paradoxical reactions in 50 HIV-infected patients receiving TB treatment. Of the 50, 28 commenced ART after TB treatment and 8 of these developed paradoxical TB-IRIS. Data shown are for these 8 patients.
This paper reported on 57 cases of TB, MAC and cryptococcal IRIS (26 of 57 were TB-IRIS). 5 of these 57 patients started 
ART before the opportunistic infection was diagnosed, and were thus not paradoxical IRIS cases. The data shown here relate to 
all 57 patients.

14 TB-IRIS cases were reported. 9 of these were paradoxical TB-IRIS cases. Data shown are for all 14 cases, except interval 
ART to IRIS which is for paradoxical cases only.
Table 3: Diagnostic check list for paradoxical TB-IRIS

<table>
<thead>
<tr>
<th>A) Both antecedant requirements must be met</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) The TB diagnosis was made before starting ART and fulfils WHO criteria</td>
</tr>
<tr>
<td>2) The patient’s condition should have stabilised or improved on appropriate TB treatment prior to ART initiation (unless ART was started within 2 weeks of TB treatment).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B) Clinical criteria should be fulfilled</th>
</tr>
</thead>
<tbody>
<tr>
<td>The onset of manifestations is within 3 months of ART initiation, re-initiation, or regimen change due to treatment failure.</td>
</tr>
<tr>
<td>At least 1 major criterion or 2 minor clinical criteria are required.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) New or enlarging lymph nodes, cold abscesses or other focal tissue involvement</td>
</tr>
<tr>
<td>2) New or worsening radiological features of TB</td>
</tr>
<tr>
<td>3) New or worsening central nervous system TB</td>
</tr>
<tr>
<td>4) New or worsening serositis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) New or worsening constitutional symptoms</td>
</tr>
<tr>
<td>2) New or worsening respiratory symptoms</td>
</tr>
<tr>
<td>3) New or worsening abdominal pain accompanied by peritonitis or hepatomegaly or splenomegaly or abdominal adenopathy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C) Alternative explanations for clinical deterioration must be excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Failure of TB treatment due to TB drug resistance</td>
</tr>
<tr>
<td>2) Poor adherence to TB treatment</td>
</tr>
<tr>
<td>3) Another opportunistic infection or neoplasm.</td>
</tr>
<tr>
<td>4) Drug toxicity or reaction</td>
</tr>
</tbody>
</table>
Figure 1. Delegates at the Kampala TB-IRIS meeting, November 2006.
Figure 2. Illustrative case of ‘paradoxical TB-IRIS’: A 36-year old HIV-infected man was diagnosed with culture-positive pulmonary tuberculosis (sensitive to rifampin and isoniazid) without evidence of extrapulmonary involvement. His CD4 count was 39 cells/μL and HIV-1 viral load (VL) 1,300,000 copies/ml. He commenced antiretroviral therapy (ART) 7 weeks after initiating antituberculous therapy. One week later he presented with a recurrence of TB symptoms and cervical node enlargement. Paradoxical TB-IRIS was diagnosed. Over the next 18 months he presented with several TB-IRIS manifestations which sequentially emerged, despite corticosteroid therapy, then resolved. Photographs show development of massive cervical lymphadenitis (a), a chest wall cold abscess (b - arrowed) and a massive right psoas abscess shown here on CT scan (c – arrowed) from which over 2 litres of pus was aspirated (d). Repeated mycobacterial cultures of aspirates from these collections have been negative. After 6 months on ART his CD4 cell count was 181 cells/μL and VL undetectable. After 12 months his CD4 was 448 cells/μL and VL 35 copies/mL. This was an unusually prolonged course for ‘paradoxical TB-IRIS’ given that the median duration of symptoms is reported to be 2 months.
Figure 3. Illustrative case of unmasking TB-IRIS’: A 48 year old HIV-infected man with a CD4 count of 10 cells/µL presented with low grade fevers, retro-sternal 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 TB were available in this resource-constrained setting. Antiretroviral therapy (ART) was started (zidovudine, lamivudine and efavirenz). Ten 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 revealed left midzone consolidation (b) and his sputum
was positive for acid-fast bacilli. The unusual rapidity and clinical severity of his TB
presentation was attributed to ‘unmasking TB-IRIS’. He responded well to continued
ART and TB treatment.
Figure 4. Schematic representation illustrating the different forms of TB immune reconstitution inflammatory syndrome (TB-IRIS) and ART-associated TB.
TB diagnosed and TB treatment started prior to ART initiation

Not on TB treatment when ART is initiated

ART INITIATED

Paradoxical reaction within 3 months
= paradoxical TB-IRIS

Active TB diagnosed on ART
= ART-associated TB

(A subset these patients may have unmasking TB-IRIS)

Figure 4.
REFERENCES
