Tuberculosis immune reconstitution inflammatory syndrome: profile of an enigmatic condition

G. Narendran and S. Swaminathan*
National Institute for Research in Tuberculosis, 1, Mayor Sathyamoorthy Road, Chetpet, Chennai 600 031, India

Tuberculosis Immune Reconstitution Inflammatory Syndrome (TB-IRIS) in HIV co-infected TB patients is an intriguing but frequently occurring phenomenon experienced by patients after initiating anti retroviral therapy. It is characterized by paradoxical worsening of clinical and radiological manifestations of TB, after initiation of highly active antiretroviral therapy, when improvement in the general condition of the patient is usually anticipated. This paradoxical reaction is brought about by a cascade of inflammatory reactions triggered by the recovery of the immune system both in quality and quantity. Manifestations of TB-IRIS range from mild self-limiting symptoms to life-threatening compressive syndromes that could rarely be fatal. Often, this condition is confused with treatment failure or drug toxicity, which could lead to unnecessary drug interruption or substitution. Recognition of this syndrome assumes significance in the context of these two diseases, which mandate prolonged therapy with very high adherence to achieve the desired results. This article provides an overview of the risk factors, pathogenesis, clinical presentation, available diagnostic tools and treatment strategies for TB-IRIS with implications for patients and personnel involved in TB/HIV care.

Keywords: Antiretroviral therapy, immune reconstitution inflammatory syndrome, paradoxical reaction, tuberculosis.

Introduction

Tuberculosis Immune Reconstitution Inflammatory Syndrome (TB-IRIS) or paradoxical reaction is a phenomenon that frequently complicates the management of HIV–TB co-infected persons. It is characterized by an initial improvement with anti-tuberculosis treatment (ATT), followed by a paradoxical worsening after initiation of antiretroviral treatment (ART), despite effective virological suppression and control of both infections. With current scientific evidence favouring the initiation of ART as early as possible in HIV–TB co-infected patients on ATT, the prevalence is likely to increase further. TB-IRIS accounts for at least one third of all IRIS events in HIV-infected patients in countries with a high prevalence of TB, with the frequency of occurrence and severity increasing with immunosuppression. The HTPN052 trial was aimed at studying the advantages of starting highly active antiretroviral therapy (HAART) in HIV-infected patients at a higher CD4 cell count (500 cells/mm³); this could serve as an effective prevention strategy not only against occurrence of opportunistic infections but IRIS as well. TB patients initiated on ART, when CD4 cell count is relatively high, have a better outcome with lower probability of drug toxicity and IRIS incidence when compared to patients with lower CD4 cell count at ART initiation. Hence, the current National AIDS Control Organisation (NACO) guidelines emphasize the need for early ART initiation in all HIV/TB patients, irrespective of their CD4 cell count. However, the reality is that HIV infection, in its early stages is usually cryptic producing non-specific symptoms. The diagnosis of HIV is often coupled with TB, the commonest opportunistic infection in India among HIV-infected individuals. Trials conducted at the National Institute for Research in Tuberculosis (NIRT), Chennai, have shown that approximately two-thirds of HIV–TB co-infected patients at the time of enrollment are in WHO stage IV, with an already depleted CD4 cell count below 200 cells/mm³. A study from Pune showed that CD4 count was considerably lower in patients, who presented themselves with combined pulmonary and extra pulmonary TB compared to patients with TB confined to the lungs.

TB-IRIS is of two types: (a) paradoxical TB-IRIS that occurs in patients started on ATT and subsequently started on ART and (b) unmasking TB-IRIS or ART associated TB that occurs in seemingly asymptomatic individuals, who are initiated on ART without a prior diagnosis of TB. Management of both these conditions differs widely. In this review, we confine ourselves to a detailed description of the paradoxical type of TB-IRIS and highlight the important aspects of TB-IRIS including, possible risk factors, clinical features, diagnosis, clinical conditions that simulate IRIS and management. IRIS management requires expertise and if not detected early, could lead to increased morbidity and mortality, incurring...
Table 1. Incidence of TB-IRIS in HIV–TB co-infection in various cohorts

<table>
<thead>
<tr>
<th>Study investigator/year</th>
<th>Design of the study and type of TB in the cohort</th>
<th>Year studied</th>
<th>Incidence of TB-IRIS (%)</th>
<th>Median age of patients (years)</th>
<th>Median CD4 at baseline (cells/mm³)</th>
<th>Median VL in at baseline (log₁₀/ml)</th>
<th>Median time from TB diagnosis/treatment to IRIS in days</th>
<th>Median time from start of ART to IRIS in days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narita et al.¹², 1998</td>
<td>Prospective cohort, culture proved TB, including Rif resistant TB</td>
<td>1996–1997</td>
<td>12/33 (36%)</td>
<td>40*</td>
<td>51*</td>
<td>5.8</td>
<td>109</td>
<td>15</td>
</tr>
<tr>
<td>Breton et al.²⁹, 2004</td>
<td>Retrospective cohort, clinical, radiological TB; smear and culture positive TB</td>
<td>1996–2001</td>
<td>16/37 (43%)</td>
<td>35</td>
<td>100</td>
<td>5.36</td>
<td>48</td>
<td>12</td>
</tr>
<tr>
<td>Breen et al.¹⁵, 2004</td>
<td>Retrospective study, bacteriological and histological evidence of TB</td>
<td>1997–2002</td>
<td>14/50 (35%)</td>
<td>36</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>33</td>
</tr>
<tr>
<td>Kumaraswamy et al.¹⁴, 2004</td>
<td>Retrospective cohort, clinical, radiological TB; smear and culture positive TB</td>
<td>2000–2003</td>
<td>11/144 (8%)</td>
<td>29</td>
<td>123</td>
<td>NA</td>
<td>NA</td>
<td>42</td>
</tr>
<tr>
<td>Manosuthi et al.³⁷, 2006</td>
<td>Retrospective cohort, clinical, radiological TB; smear and culture positive TB</td>
<td>2003–2004</td>
<td>21/167 (21%)</td>
<td>36</td>
<td>36</td>
<td>5.63</td>
<td>98</td>
<td>32</td>
</tr>
<tr>
<td>Lawn et al.¹³, 2007</td>
<td>Newly diagnosed TB and patients on ATT</td>
<td>2002–2005</td>
<td>19/160 (13%)</td>
<td>35</td>
<td>68</td>
<td>4.84</td>
<td>105</td>
<td>14</td>
</tr>
<tr>
<td>Worodria et al.¹⁴, 2012</td>
<td>Prospective cohort bacteriological, clinical, radiological TB</td>
<td>2007–2009</td>
<td>53/376 (21%)</td>
<td>35</td>
<td>52</td>
<td>NA</td>
<td>NA</td>
<td>58</td>
</tr>
<tr>
<td>Narendran et al.¹⁴, ongoing</td>
<td>Prospective cohort of culture positive rifampicin sensitive pulmonary TB</td>
<td>2009–ongoing</td>
<td>65/180 (36%)</td>
<td>42</td>
<td>85</td>
<td>5.2</td>
<td>32</td>
<td>9</td>
</tr>
</tbody>
</table>

large costs to the health system by increased utilization of tertiary care facilities.

Prompt institution of anti-inflammatory drugs, usually corticosteroids, drastically alleviates the symptoms and signs, whereas unrecognized IRIS proves detrimental to patients. Non-adherence could occur due to drug phobia, brought about by initiation of ART, that could result in emergence of ATT and/or ART drug-resistant strains and an increased risk of developing treatment failure³.

**Increasing IRIS incidence**

Paradoxical IRIS is easier to recognize than the unmasking type, because it follows a biphasic pattern of presentation; an initial phase of improvement with ATT followed by ‘paradoxical’ deterioration after ART initiation. This occurs despite effective virological suppression and in most cases, is associated with good immune recovery. Before the HIV era, reports of paradoxical reactions or IRIS were confined to specific types of TB such as tuberculoma of the brain and peripheral lymphadenopathy¹². Radiological worsening in pulmonary TB, with or without worsening of symptoms or ‘cryptic IRIS’, was reported in studies of TB chemotherapy in the pre-HIV era¹³. However, the incidence of TB-IRIS doubled with the advent of HIV and further increased with earlier ART initiation¹²,¹⁴. A comparison of three groups of HIV–TB patients enrolled in three separate clinical trials had an incidence of 2%, 21%, 36% when ART was started (a) after completion of ATT, (b) after 2 months of ATT and (c) within the first 2 months of ATT respectively³,¹⁰,¹⁴. Table 1 gives a detailed description of the baseline characteristics of HIV–TB patients enrolled in various studies from around the globe with data on timing of ART, immune status and the corresponding incidence of paradoxical TB-IRIS. A constant finding in all these studies is the higher incidence of IRIS when the interval between ATT and ART is shorter¹²,¹⁴–¹⁶.

**Risk factors for TB-IRIS – who is vulnerable and what predisposes to IRIS?**

IRIS occurs with greater severity and increased frequency in patients with disseminated TB or pulmonary TB with an occult/overt extra-pulmonary focus, in whom, a severe depletion of CD4 cell count is an associated feature. Presence of other opportunistic infections in addition to TB increases the risk. The increased antigenic load contributed by extensive disease and multiple sites of involvement with a higher viral load at baseline is the
major predisposing factor for IRIS\textsuperscript{3,6,7,17}. Studies reveal that the rapidity of viral load decline, rather than the proportionate increase in absolute number of CD4 cells is the prime culprit, leading to unimpeded release of inflammatory mediators contributing to IRIS occurrence\textsuperscript{18}. The risk factors and sequence of events leading to IRIS occurrence are shown in Figure 1. To evaluate baseline differences and search for predictive markers between patients who experienced IRIS (IRIS cases) and those who remained asymptomatic (non-IRIS) a cohort of HIV-positive patients with culture confirmed pulmonary TB was prospectively followed. Results showed evidence of more advanced stages of the disease and shorter time to ART among patients who developed IRIS compared to those who did not\textsuperscript{19} (Table 2).

**Pathogenesis of TB-IRIS: how and why does it occur? The influence of functional restoration of immune-competent cells**

An enigmatic fact is that certain patients have a significant increase in CD4 cell count without experiencing IRIS while others exhibit symptoms and signs of IRIS without a corresponding increase in CD4 cell count. Preliminary work on IRIS suggested that it occurred due to an increase in the number of CD4 cells after ART, which induced an exaggerated Th1 type of immune response\textsuperscript{12}. However, it is not uncommon for IRIS to present within the first two weeks of starting ART when there is no demonstratable increase in the number of circulating CD4 cells\textsuperscript{18}. The explanation lies in the fact that the increase in CD4 cell count occurs in a bimodal fashion. The initial phase consists of a rapid increase in circulating cells representing a redistribution of activated CD45RO memory cells, followed by a slow and steady expansion of naïve CD45RA cells when thymic function is restored that accounts for the sustained rise in CD4 cell count\textsuperscript{18}. The majority of paradoxical IRIS cases occur within the first three months after starting ART due to the increase in CD45RO memory cells. Redistribution of these cells augments antigen specific responses, as they gain access to the site of infection, triggering an inflammatory cascade\textsuperscript{19}. Functional restoration of the immune system has a bigger role to play in IRIS pathogenesis than a mere increase in numbers\textsuperscript{3,18,20}.

**Cytokine storm and exaggerated Th-1 response – ‘the ammunition in IRIS’**

IRIS occurs due to an exaggerated TB-specific Th-1 response to mycobacterial antigens as a result of immune restoration\textsuperscript{20}. Bourgarit \textit{et al.}\textsuperscript{21} showed that the unopposed PPD-specific Th-1 response with minimal Th2 activity leads to acute release of pro-inflammatory cytokines, resulting in IRIS. Increased interleukin-7 (IL-7) signaling in T cells, owing to the lack of competition for this cytokine in driving homeostatic proliferation of T cells in lymphopenia, has also been implicated\textsuperscript{22}. The probable cytokines that contribute to the inflammation along with the risk factors have been shown in Figure 2. Tadokera \textit{et al.}\textsuperscript{23} confirmed that the cytokine storm was indeed the preceding event, by not only demonstrating the increased levels of cytokines at symptom presentation, but showing the decrease when steroids were administered. Sereti \textit{et al.}\textsuperscript{24} showed that circulating T-cells produced increased interferon-gamma in response to antigenic stimulation of CD4 cells \textit{in vitro} (that was demonstrated using enzyme linked immunospot assay or whole blood IFN-gamma release assays (IGRAs) and flow cytometric analysis of intracellular cytokine production in activated T cells). Production of monocyte chemotactic protein-1, that aids in chemotaxis of monocytes, was reduced in TB-IRIS patients, whereas interleukin-18 a macrophage derived inducer of IFN-gamma and IFN-gamma inducible protein (IP-10), which is chemotactic
SPECIAL SECTION: TUBERCULOSIS

Table 2. Comparison of baseline characteristics between IRIS and non-IRIS among culture confirmed pulmonary TB patients who were ATT and ART naïve at enrollment19

<table>
<thead>
<tr>
<th>Baseline characteristics (mean ± SD)</th>
<th>IRIS (n = 25)</th>
<th>Non-IRIS (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37.7 ± 9.8</td>
<td>36.2 ± 7.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>43.4 ± 8.8</td>
<td>42.7 ± 9.6</td>
</tr>
<tr>
<td>Males (%)</td>
<td>76</td>
<td>81</td>
</tr>
<tr>
<td>Hemoglobin (g%)*</td>
<td>8.7 ± 1.8</td>
<td>10.4 ± 1.9</td>
</tr>
<tr>
<td>Hematocrit (%)**</td>
<td>25.5 ± 5.9</td>
<td>30.0 ± 5.7</td>
</tr>
<tr>
<td>Viral load (log_{10} copies/ml)***</td>
<td>5.8 ± 0.33</td>
<td>5.2 ± 0.91</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm³) median (IQR)</td>
<td>93 (39–155)</td>
<td>156 (88–264)</td>
</tr>
<tr>
<td>CD8 cell count (cells/mm³) median (IQR)</td>
<td>764 (311–1095)</td>
<td>459 (297–727)</td>
</tr>
<tr>
<td>CD4/CD8 ratio*** median (IQR)</td>
<td>0.10 (0.05–0.18)</td>
<td>0.34 (0.21–0.47)</td>
</tr>
<tr>
<td>Time to ART* (in days) median (IQR)</td>
<td>20 (14–30)</td>
<td>43 (23–68)</td>
</tr>
</tbody>
</table>

*a p < 0.05; **p < 0.01; ***p < 0.001.

Figure 2. A, Chest skiagrams of a miliary TB patient showing radiological improvement with ATT and paradoxical worsening with ART and again clearance of opacities after steroids. a, PRE_ATT; b, PRE_ART (after 6 weeks of ATT); c, AT IRIS; d, AFTER STEROIDS. B, Diverse manifestations of IRIS in different patients. a, Massive right para tracheal lymphadenopathy with pleural effusion, presenting as stridor; b, Multiple tuberculoma brain; c, Cold abscess mimicking a thyroid swelling; d, Enlarged peri-portal chain of lymph nodes.

for effector T cells was increased in blood. This suggests that impaired clearance of mycobacterial antigenic load with augmented T-cell signalling and responses contribute to IRIS24. Another study of tuberculosis-associated IRIS in individuals infected with HIV found that whole-blood cultures from patients with IRIS spontaneously (that is, without any sort of in vitro stimulation) produced increased levels of innate immune cell-derived cytokines and chemokines25. Our data from NIRT shows that interleukin-6 and C-reactive protein are elevated in patients with IRIS both at baseline and at the time of IRIS, compared to patients not experiencing IRIS, implicating their role as possible predictors of IRIS occurrence19.

On the contrary, Zaidi et al.26 demonstrated that the development of IRIS was not associated with differences in levels of T regulatory cells or baseline pro-inflammatory cytokines.

**Diagnosis of IRIS and criteria used: tools that one can reasonably rely on**

Diagnosis of IRIS is still clinically based, supplemented by laboratory tests such as CD4 cell count and viral load. It is important for physicians to remember that the onset of this syndrome is chronologically linked to ART initiation, substitution or interruption followed by re-initiation3,27. A patient failing first line ART therapy may experience an IRIS episode after second line ART therapy is initiated, when there is an effective decline in viral load6. The confirmatory feature favouring the diagnosis...
of paradoxical TB-IRIS is the bimodal pattern with initial improvement with ATT followed by recrudescence of symptoms (mimicking clinical deterioration) after starting ART. Adherence to therapy needs to be ensured before establishing the diagnosis. In any case, routine work up of febrile episodes to rule out endemic infections like malaria, urinary tract infection, typhoid, etc. should be carried out. Radiological deterioration in chest skigram is a usual accompaniment in most cases of IRIS, that occurs with proven pulmonary TB. Ultra sonogram of the abdomen and chest helps in localizing lesions in patients presenting with pyrexia of unknown origin (PUO). Computed tomography may be required in complicated cases such as collapse of a lung segment or a lobe due to compression. Mediastinal mass lesion, empyema, abscesses, rib erosion, oseomyelitis and intrabdominal lesions that are not picked up by the ultrasoundogram or the chest skigram must be evaluated. Magnetic resonance imaging is useful in detecting lesions of the central nervous system as the location of the lesion determines the severity and type of manifestations that guides management. In patients who have adenopathy, serositis, etc., where a tissue/fluid specimen is available, it needs to be aspirated or biopsied and sent for bacteriological staining in addition to Fine Needle Aspiration Cytology or histopathology. Mycobacterium tuberculosis should be cultured where facilities exist, as smears can be positive, but the corresponding cultures are usually negative at IRIS. Dead or non-viable bacilli that are excreted during the intense inflammation result in the smear being positive. A negative mycobacterial culture, especially when the preexisting or baseline culture was positive and sensitive to first line drugs, helps to clinch the diagnosis. CD4 cell count and viral load estimation form the corner stone of laboratory evaluation for establishing the diagnosis with the latter taking precedence as CD4 cells may increase only after a lag period. Concomitant decrease in plasma viremia is mandatory to demonstrate effective virological suppression to establish the diagnosis of IRIS beyond doubt and to differentiate from progression of HIV disease. A decline of viral load less than 0.5 log10 copies/ml compared to baseline has a high negative predictive value in ruling out IRIS. Delayed hypersensitivity reaction using purified protein derivative (PPD), an in-vivo marker of T-cell activity, is also of value in proving IRIS. Patients who are PPD negative at start of ART become PPD positive at the time of IRIS. Hypercalcemia is a strange accompani-

Table 3. International network for the study of HIV-associated IRIS (INSHI)

Case definition consists of three components

(A) Antecedent requirements
Both of the two following requirements must be met:
- Diagnosis of tuberculosis: the tuberculosis diagnosis made before starting ART, fulfilling the WHO criteria for diagnosis of smear-positive pulmonary tuberculosis, smear-negative pulmonary tuberculosis, or extra pulmonary tuberculosis
- Initial response to tuberculosis treatment: the patient’s condition should have stabilized or improved on appropriate tuberculosis treatment before ART initiation – e.g. cessation of night sweats, fevers, cough and 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, re-initiation 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 – e.g. tuberculosis arthritis or tenosynovitis
- New or worsening radiological features of tuberculosis (by chest radiography, abdominal and chest ultrasonography, CT or MRI)
- New or worsening CNS tuberculosis (meningitis or focal neurological deficit due to space occupying lesions)
- 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, breathlessness or compressive symptoms such as stridor or dysphagia
- New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly or abdominal adenopathy

(C) Alternative explanations for clinical deterioration must be excluded if possible*
- Failures; TB not responding to ATT due to drug resistant strains or virological failures with increasing viral load (where facilities are available)
- Poor adherence to tuberculosis treatment
- Another opportunistic infection or neoplasm (particularly when the initial diagnosis of TB has not been bacteriologically confirmed)
- Adverse drug reaction to ATT or ART

SPECIAL SECTION: TUBERCULOSIS
ment of TB-IRIS caused by increased secretion of 1,25-
dihydroxy chole-calciferol by activated macrophages and
CD4 T cells, that augments calcium absorption. Among
22 patients who were at risk for paradoxical TB-IRIS
when starting ART in a South African study, a positive
urinary LAM assay at baseline was observed in all five
patients who developed TB-IRIS and in one among the
remaining 17 patients who did not have TB-IRIS.

The International Network Society for Study of HIV-
associated IRIS (INSHI) in 2008 came up with a practical
definition that could be used in resource limited settings
(Table 3). Manosuthi et al. compared the French and the
INSHI definitions and found a high concordance between
the definitions with good sensitivity and specificity. A
reasonable clause to include in the definition is the time
interval from ART to IRIS, which is usually within three
months, unless there is ART interruption followed by
re-initiation. Retrospective evaluation of INSHI criteria
among 333 IRIS patients showed INSHI definitions to be
extremely useful in identification of IRIS.

Clinical features of TB-IRIS

Manifestations of paradoxical IRIS are diverse (Figure
2A and B). The commonest and most consistent symptom
is fever with rigour or chills closely resembling malaria
and the commonest sign is lymph node enlargement that
occurs in 75% of cases with or without associated intra-
thoracic adenopathy (20%). Worsening of parenchymal
infiltrates on the chest skiagram is the second commonest
manifestation (Figure 2A). Presentations may vary
from mere superficial lymphadenopathy and subcutaneous
abscesses to severe forms like acute respiratory distress
syndrome (ARDS), meningitis, space-occupying lesions
like tuberculomas and vescic perforation which can end
fatally. Compensatory syndromes due to lymphadenopa-
thy may manifest as stridor due to tracheal narrowing or
superior vena caval (SVC) syndrome due to compression
of SVC by upper mediastinal group of nodes. Serositis is
also not infrequent. The severity and diversity of symp-
toms and signs depend on the site of infection. Patients
with abdominal TB suffer from pain and diarrhoea. Other
abdominal manifestations include hepato-splenomegaly,
psosas abscesses, splenic micro abscesses, splenic rupture,
epididymoorchitis, uretric compression and acute renal
failure. Occurrence of osteomyelitis, sub-cutaneous
abscesses and throboembolic episodes have been report-
ed. A NRT study of HIV–TB patients showed that
radiographic deterioration was present in 40% and extra-
pulmonary manifestations in 60% of patients experienc-
ing paradoxical TB-IRIS. In the same study, patients with
IRIS presented with lymph node enlargement in one
third, 23% had pleural effusion and one patient had tu-
berculoma brain. None died due to IRIS. Meintjes et al.
reported 59% had abdominal symptoms, 56% of the
patients had hepatomegaly, 9% had splenomegaly and 5%
had peritonitis. Ultrasonogram of the abdomen detected
enlarged lymph nodes in 75% of the patients.

Differential diagnosis of IRIS: the ‘close relatives of
IRIS’ that need exclusion

Multi-drug resistant TB (MDR-TB) is the closest mimic
to TB-IRIS. HIV–TB co-infected individuals have a
higher propensity for emergence of multidrug resistant
TB than individuals with TB alone. HIV enteropathy
impairs absorption and diarrhea by entero-pathogenic
organisms shortens the gastro-intestinal transit time lead-
ing to mal-absorption and sub-therapeutic dosing. A
higher tissue burden of bacilli due to defective clearance
imposed by immuno-deficiency coupled with a subopti-
mal dosage of ATT provides an ideal scenario for emer-
gence of drug-resistant mutants. The initial bacterial
population may decline as a result of drug-sensitive ba-
cilli succumbing to ATT, which is progressively replaced
by drug-resistant mutants that rise in a couple of months.
This phenomenon described by Toman as the ‘fall and
rise phenomenon’ typically mimics the bimodal pattern
of improvement followed by deterioration that occurs in
IRIS. A study of HIV–TB co-infected patients con-
ducted in the pre-HAART era showed a 10% incidence of
rifampicin resistance when they failed ATT. Meintjes et al.
showed that 10% of their cohort who presented as
TB-IRIS were actually MDR-TB cases. IRIS in MDR-TB
is not a rarity and they are not mutually exclusive
either. Exclusion of MDR-TB is an absolute priority
when use of steroids is contemplated. Steroids which re-
main the cornerstone of treatment could spell disaster in
the scenario of MDR-TB, ending fatally. The program-
matic management of MDR-TB (PMDT) guidelines pro-
moting the use of rapid molecular tests to detect drug
resistance in all HIV patients with TB, may help in diag-
nosing primary MDR-TB earlier, so that the two may be
easily differentiated and managed accordingly.

With the phase out of stavudine from the ART pro-
colgue, due to its side effects including lipodystrophy
and dyslipaemia, zidovudine based regimes have become
the main stay of HIV management in India. Zido-
vudine-induced anemia also simulates IRIS, as it mimics
the same symptoms as IRIS. The incidence of zidovu-
dine-induced anemia in an ongoing RCT showed a 7%
incidence in HIV–TB with 3/4th of the patients present-
ing themselves with fever and rigour that settled after
withdrawing zidovudine. Patients with IRIS occurring
after 3 months of ART initiation (late onset IRIS) need to
be differentiated from ART failure and HIV progression
by sequential estimation of viral load. Viral load is
usually undetectable in late onset IRIS.

Lymphoma of the non-Hodgkins type commonly affects
HIV patients. This condition could flare up in HIV

SPECIAL SECTION: TUBERCULOSIS
patients after ART and may be misdiagnosed as TB-IRIS. Lymphoma and TB are known to co-exist. Hence, what appears as TB-IRIS of the lymph node may turn out to be ‘unmasking IRIS’ of lymphoma. Other important differential diagnoses include infection with nontuberculous mycobacteria especially Mycobacterium Avium Intracellulare, Pneumocystis Carinii Pneumoniae, Cryptococcus and Nocardia. Nocardia being partially acid fast, mimics TB not only in presentation such as serosal involvement and chest wall abscesses, but also in microscopic findings.

Management

Most HIV-infected patients in developing countries approach health care systems only when an opportunistic infection like TB occurs. They are usually at an advanced stage of immunodeficiency at presentation. Recent WHO guidelines recommend ART initiation at a higher CD4 cell cut off of 500 cells/mm³, compared to the previous 350 cells/mm³ (ref. 44). Haddow et al demonstrated that the increase in CD4 cell count by 50 cells during ART initiation, the risk of experiencing IRIS was reduced by 17% (95% CI 6–26%), with a 43% reduction in all cause mortality. Therefore, earlier initiation of ART would lead to lower IRIS incidence in future.

An interesting fact is that long-term Cotrimoxazole therapy prior to ART reduced IRIS events compared to concurrently starting it with ART, probably by reducing the incidence of other opportunistic infections. Meticulous screening for opportunistic infections including TB prior to ART initiation would be the second preventive step against IRIS. This is especially so in countries endemic for TB and cryptococcosis that are associated with significant morbidity and mortality. Detection of latent TB, extra-pulmonary TB and smear negative TB in HIV, especially in the setting of profound lymphopenia is challenging, but expanding access to more sensitive tools like Xpert MTB/rif and other rapid molecular tests, should help.

Optimal timing of ART in the context of TB–HIV co-infection

One practical solution to the problem of IRIS occurrence is optimizing the time of ART initiation with respect to ATT. Physicians need to strike a balance between delaying ART and its impact on survival, weighed against the odds of developing IRIS when ART is started early. The flexibility offered in the NACO guidelines to start patients on ART in HIV–TB co-infection within a span of 2–8 weeks after ATT, may prove beneficial in tackling this problem. Three major studies on timing of ART in HIV–TB co-infection have provided important insights in maximizing survival benefits while reducing the risk of IRIS. The SAPIT study (South African Starting Antiretroviral Therapy at Three Points in Tuberculosis Therapy) concluded that initiation of ART within the intensive phase was necessary to reduce mortality by half (56%) among HIV–TB co-infected patients on ATT compared to starting ART after 6 months (ATT completion). However, among patients starting ART within the first month of ATT, a three times higher incidence of IRIS and 90% more incidence of toxicity was documented, when compared to those patients starting ART at the end of 2 months, without any additional survival benefits. ACTG 5221 clinical trial enrolled 809 patients with a median CD4 cell count of 77 cells/mm³ and a median viral load of 5.4 log₁₀ copies/ml. Unfavourable response (mortality or AIDS defining illness) was 12.6% in the early ART group versus 16.1% in the late ART group (p = 0.45). But the incidence of IRIS was reduced to half in the late ART group. Viral load suppression at the end of 48 weeks was equivalent in both the groups. The clear cut survival benefit of early ART initiation, within 2 weeks of starting ATT was evident only in the group that had a CD4 cell count < 50 cells/mm³ (ref. 49).

The CAMELIA study (Cambodian Early versus Late Introduction of Antiretrovirals) initiated ART among dually infected patients within two weeks of ATT in one group and between 8 and 12 weeks in the other group. Mortality was reduced in the former group. However, the overall median CD4 cell count of the study subjects enrolled in this Cambodian study, was only 25 cells/mm³, confirming the benefit of early ART in patients with advanced disease. NIRT experience among HIV–TB dually infected subjects showed an overall mortality of 14.7% when started at 2 months compared to 8.3% when it was initiated in the intensive phase (p = 0.07). However, the incidence of IRIS was 20% with later ART compared to 38% when started within the intensive phase (p = 0.01). The key message from the findings of the above studies, conducted in different settings, is that among patients with CD4 cell count of more than 50 cells, deferral of ART after the first few weeks of ATT helped in reducing toxicity and IRIS without compromising on survival. There are however exceptions to this rule. Study by Torok et al. on tuberculous meningitis found that the immediate ART group had a higher incidence of grade 4 adverse reactions and IRIS, compared to the delayed group that started ART at 2 months without an accompanying survival advantage. It should be emphasized that individualized therapy taking into account the stage of the disease and facilities available for tackling IRIS would serve as the best option.

Treatment

Paradoxical IRIS is usually associated with considerable morbidity and substantial utilization of tertiary care servi-
ces, requiring appropriate experts to manage this syndrome effectively. Anti-inflammatory drugs form the backbone of the therapy, starting with non-steroidal anti-inflammatory agents being the agents of first choice. Steroids, the principal therapy for IRIS management, have been used in more than a third of the case. Manabe et al. reported 75% of patients experiencing IRIS required steroid therapy. A dose of 0.5–2 mg/kg body weight, tapered over a period of 4–8 weeks depending on the site and severity of the disease is usually recommended. Manifestations of IRIS such as aseptic meningitis, pericardial effusion, mediastinal adenopathy with compression, acute respiratory distress syndrome, etc. may require parenteral steroids like hydrocortisone, methyl prednisolone or dexamethasone to start with, followed by switch to oral prednisolone. Deflazacort, a prodrug derivative of prednisolone, is a proven alternative in children with reduced suppression of the limbic system and interference of the circadian rhythm of endogenous steroid production. Its higher potency and greater safety profile with lower osteoporotic and diabetogenic potential makes it ideal for use in children, especially when long-term therapy is contemplated. A double-blind study conducted in South Africa using three months of steroids and placebo in TB-IRIS showed a reduced duration of hospital stay, faster clinical improvement and greater radiological improvement in the steroid group. Side effects due to immunological suppression in the form of new infections were slightly more in the steroid arm, but without appreciable morbidity. Thalidomide, another potent anti-inflammatory drug, has been used for refractory or relapsing IRIS cases and in patients who eventually become steroid dependent in order to wean them off steroids. Anecdotal reports of pentoxifylline and montelukast (a leukotriene inhibitor) used for the treatment of IRIS have been published, but routine use and benefits have not been explicitly determined. The role of leukotriene pathways in the pathogenesis of IRIS need to be established before contemplating on routine use of leukotriene antagonists for treatment of TB-IRIS in clinical practice. Rarely, uncontrolled and life threatening IRIS cases need a temporary interruption of ART as a last resort, in addition to steroids. The decision to withhold ART has to be carefully evaluated after meticulous efforts to prove it as precipitating IRIS, and other alternative diagnoses have been reasonably excluded. Patients need to be closely monitored in a tertiary care facility during the ‘ART-free’ period.


ACKNOWLEDGEMENTS. We thank the members of the NIH–NIAID team, I. Sereti, A. B. Bruno, B. Porter, C. Chandrasekhar, Superintendent, Government Hospital of Thoracic Medicine (GHTM), Tambaram Sanatorium and the medical officers of GHTM, ART medical officers in Chennai and N. Shanthanakumar, Vellore and our colleagues in NRT for sharing their expertise in TB–HIV management, that helped us in drafting the manuscript.