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[1]. 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[2,3]. 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/mm^3); this could serve as an effective prevention strategy not only against occurrence of opportunistic infections but IRIS as well[4]. 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[5,6]. 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[7]. 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[8]. 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/mm^3 (refs 9 and 10). 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[11].

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[3]. 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

*For correspondence. (e-mail: soumyas@trcchennai.in)

Table 1. Incidence of TB-IRIS in HIV–TB co-infection in various cohorts

Study investigator/year	Design of the study and type of TB in the cohort	Year studied	Incidence of TB-IRIS (%)	Median age of patients (years)	Median CD4 at baseline (cells/mm^3)	Median VL in at baseline ($\log_{10}$/ml)	Median time from TB diagnosis/ treatment to IRIS in days	Median time from start of ART to IRIS in days
Narita *et al.*[12], 1998	Prospective cohort, culture proved TB, including Rif resistant TB	1996–1997	12/33 (36%)	40*	51*	5.8	109	15
Breton *et al.*[29], 2004	Retrospective cohort, clinical, radiological TB; smear and culture positive TB	1996–2001	16/37 (43%)	35	100	5.36	48	12
Breen *et al.*[15], 2004	Retrospective study, bacteriological and histological evidence of TB	1997–2002	14/50 (35%)	36	NA	NA	33	11
Kumaraswamy *et al.*[16], 2004	Retrospective cohort, clinical, radiological TB; smear and culture positive TB	2000–2003	11/144 (8%)	29	123	NA	42	22
Manosuthi *et al.*[57], 2006	Retrospective cohort, clinical, radiological TB; smear and culture positive TB	2003–2004	21/167 (21%)	36	36	5.63	98	32
Lawn *et al.*[17], 2007	Newly diagnosed TB and patients on ATT	2002–2005	19/160 (13%)	35	68	4..84	105	14
Worodria *et al.*[58], 2012	Prospective cohort bacteriological, clinical, radiological TB	2007–2009	53/376 (21%)	35	52	NA	58	14
Narendran *et al.*[14], ongoing	Prospective cohort of culture positive rifampicin sensitive pulmonary TB	2009–	65/180 (36%)	42	85	5.2	32	9

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 failure[3].

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 lymphadenopathy[12]. 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 era[13]. However, the incidence of TB-IRIS doubled with the advent of HIV and further increased with earlier ART initiation[12,14]. 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 respectively[9,10,14]. 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 shorter[12,14–16].

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[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[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[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[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[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[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[19]. Functional restoration of the immune system has a bigger role to play in IRIS pathogenesis than a mere increase in numbers[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[20]. Bourgarit *et al.*[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[22]. The probable cytokines that contribute to the inflammation along with the risk factors have been shown in Figure 2. Tadokera *et al.*[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 *et al.*[24] showed that circulating T-cells produced increased interferon-gamma in response to antigenic stimulation of CD4 cells *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

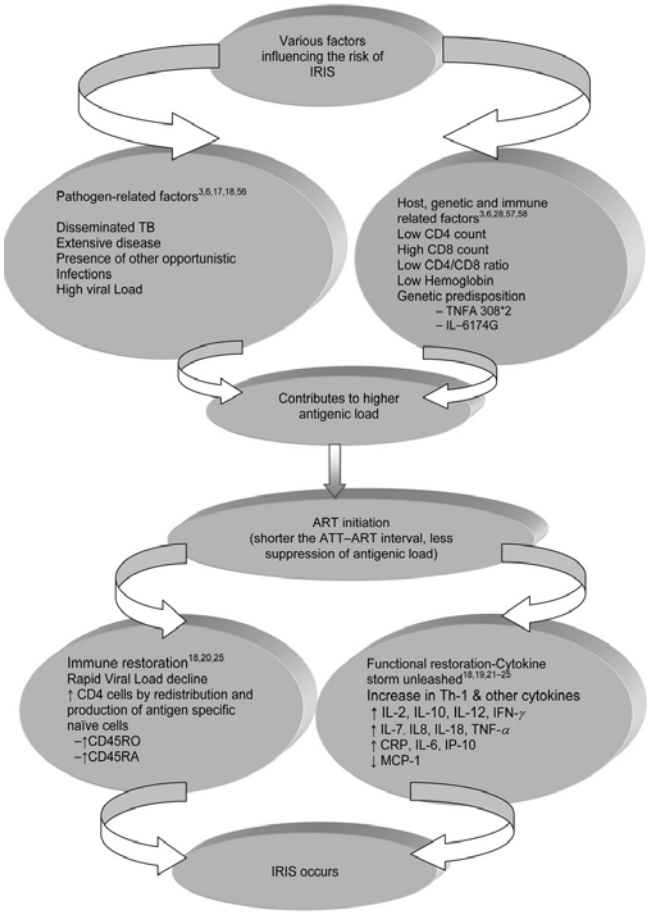

Figure 1. Flow chart depicting the risk factors and sequence of events leading to IRIS occurrence. IL, Interleukin; IFN-γ, interferon gamma; CRP, C-reactive protein; TNF-α, tumour necrosis factor alpha; MCP-1, monocyte chemotactic protein; IP-10, IFN-γ inducible protein; CD, cluster of differentiation; HB, hemoglobin; Th1, Type I helper T cell cytokines.

Table 2. Comparison of baseline characteristics between IRIS and non-IRIS among culture confirmed pulmonary TB patients who were ATT and ART naïve at enrollment[19]

Baseline characteristics (mean + SD)	IRIS (n = 25)	Non-IRIS (n = 22)
Age (years)	37.7 ± 9.8	36.2 ± 7.2
Weight (kg)	43.4 ± 8.8	42.7 ± 9.6
Males (%)	76	81
Hemoglobin (g%)*	8.7 ± 1.8	10.4 ± 1.9
Hematocrit (%)**	25.5 ± 5.9	30.0 ± 5.7
Viral load ($\log_{10}$) copies/ml***	5.8 ± 0.33	5.2 ± 0.91
CD4 cell count (cells/mm^3*) median (IQR)	93 (39–135)	156 (88–264)
CD8 cell count (cells/mm^3) median (IQR)	764 (311–1095)	459 (297–727)
CD4/CD8 ratio*** median (IQR)	0.10 (0.05–0.18)	0.34 (0.21–0.47)
Time to ART* (in days) median (IQR)	20 (14–30)	43 (23–68)

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

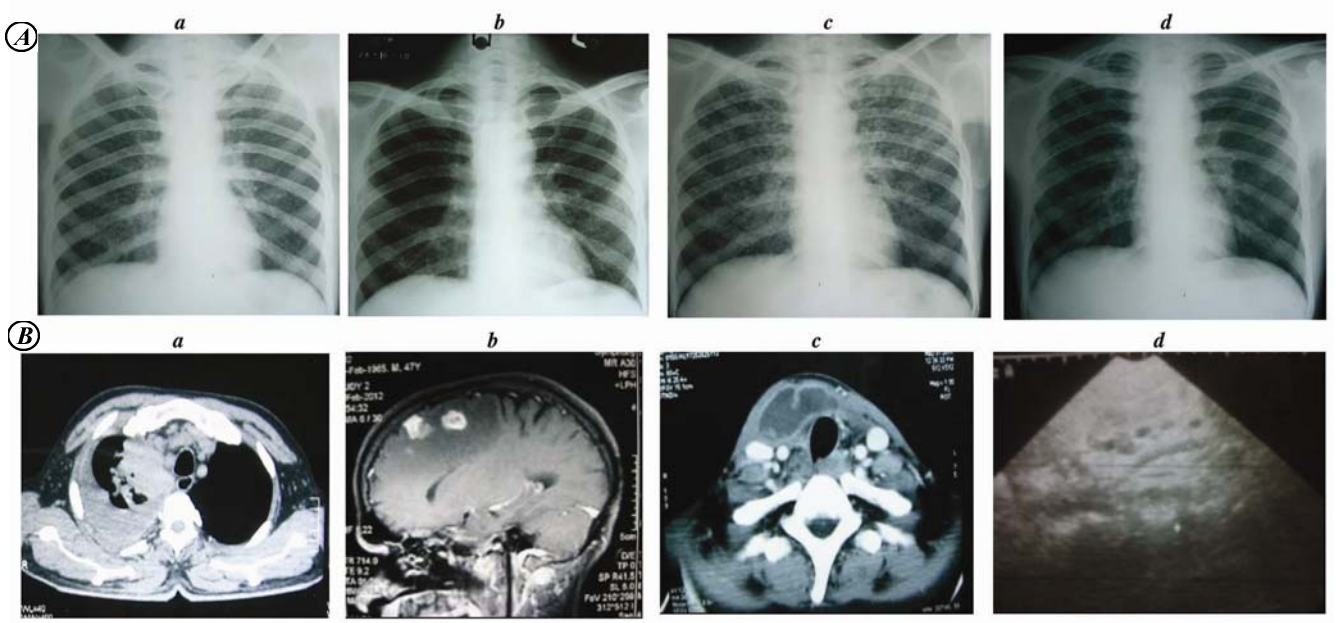

Figure 2. ***A***, Chest skiagrams of a miliary TB patient showing radiological improvement with ATT and paradoxical worsening with ART and again clearance of opacities after steroids. *a*, PRE_ATT; *b*, PRE_ART (after 6 weeks of ATT); *c*, AT IRIS; *d*, AFTER STEROIDS. ***B***, Diverse manifestations 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 IRIS[24]. 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 chemokines[25]. 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 occurrence[19].

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-initiation[3,27]. 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 load[6]. The confirmatory feature favouring the diagnosis

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

Consensus clinical case definition for paradoxical TB-IRIS (modified after Meintjes *et.al.*[3])

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

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 skiagram is a usual accompaniment in most cases of IRIS, that occurs with proven pulmonary TB[14,19]. 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 ultrasonogram or the chest skiagram 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[3,17,28]. 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[17]. A decline of viral load less than 0.5 $\log_{10}$ copies/ml compared to baseline has a high negative predictive value in ruling out IRIS[3,17,29].

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[17]. Hypercalcemia is a strange accompani-

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[27]. 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[30].

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[3] (Table 3). Manosuthi *et al.*[31] 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[32].

Clinical features of TB-IRIS

Manifestations of paradoxical IRIS are diverse (Figure 2 *A* 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%)[3,6]. Worsening of parenchymal infiltrates on the chest skiagram is the second commonest manifestation (Figure 2 *A*)[10,12]. 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 viscus perforation which can end fatally[3,6,17]. Compressive syndromes due to lymphadenopathy 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[33]. Serositis is also not infrequent[10]. The severity and diversity of symptoms and signs depend on the site of infection[29]. Patients with abdominal TB suffer from pain and diarrhoea. Other abdominal manifestations include hepato-splenomegaly, psoas abscesses, splenic micro abscesses, splenic rupture, epididymoorchitis, uretric compression and acute renal failure[3,17]. Occurrence of osteomyelitis, sub-cutaneous abscesses and thromboembolic episodes have been reported[34]. A NIRT study of HIV–TB patients showed that radiographic deterioration was present in 40% and extra-pulmonary manifestations in 60% of patients experiencing 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 tuberculoma brain. None died due to IRIS[10]. Meintjes *et al.*[34], 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[34]. HIV–TB co-infected individuals have a higher propensity for emergence of multidrug resistant TB than individuals with TB alone[35]. HIV enteropathy impairs absorption and diarrhea by entero-pathogenic organisms shortens the gastro-intestinal transit time leading to mal-absorption and sub-therapeutic dosing. A higher tissue burden of bacilli due to defective clearance imposed by immuno-deficiency coupled with a suboptimal dosage of ATT provides an ideal scenario for emergence of drug-resistant mutants[36–38]. The initial bacterial population may decline as a result of drug-sensitive bacilli 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[39]. A study of HIV–TB co-infected patients conducted in the pre-HAART era showed a 10% incidence of rifampicin resistance when they failed ATT[9]. Meintjes *et al.*[34] 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[40]. Exclusion of MDR-TB is an absolute priority when use of steroids is contemplated. Steroids which remain the cornerstone of treatment could spell disaster in the scenario of MDR-TB, ending fatally. The programmatic management of MDR-TB (PMDT) guidelines promoting the use of rapid molecular tests to detect drug resistance in all HIV patients with TB, may help in diagnosing primary MDR-TB earlier, so that the two may be easily differentiated and managed accordingly[41].

With the phase out of stavudine from the ART programme, due to its side effects including lipodystrophy and dyslipaedemia, zidovudine based regimes have become the main stay of HIV management in India. Zidovudine-induced anemia also simulates IRIS, as it mimics the same symptoms as IRIS. The incidence of zidovudine-induced anemia in an ongoing RCT showed a 7% incidence in HIV–TB with 3/4th of the patients presenting themselves with fever and rigour that settled after withdrawing zidovudine[14]. 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[6,8]. 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

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[42,43]. Other important differential diagnoses include infection with non-tuberculous mycobacteria especially Mycobacterium Avium Intracellulare, Pneumocystitis Cariini 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/mm^3, compared to the previous 350 cells/mm^3 (ref. 44). Haddow *et al.*[45] 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 Cotrimaxozole therapy prior to ART reduced IRIS events compared to concurrently starting it with ART, probably by reducing the incidence of other opportunistic infections[45]. 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[46].

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[7]. 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)[47]. 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[48]. ACTG 5221 clinical trial enrolled 809 patients with a median CD4 cell count of 77 cells/mm^3 and a median viral load of 5.4 $\log_{10}$ 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/mm^3 (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/mm^3, confirming the benefit of early ART in patients with advanced disease[50]. 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 ($p = 0.07$)[10,14]. However, the incidence of IRIS was 20% with later ART compared to 38% when started within the intensive phase ($p = 0.01$)[14,19]. 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.*[51] 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[52]. Manabe *et al.*[18] 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[3,18,52]. 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[53]. 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[52]. 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[54]. Anecdotal reports of pentoxifylline and monteleukast (a leukotriene inhibitor) used for the treatment of IRIS have been published, but routine use and benefits have not been explicitly determined[55,56]. The role of leukotriene pathways in the pathogenesis of IRIS need to be established before contemplating on routine use of leucotriene 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[3,12]. 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.

1. World Health Organization (WHO), Rapid advice: antiretroviral therapy for HIV infection in adults and adolescents. November 2009; http://www.searo.who.int/LinkFiles/HIV-AIDS_Rapid_Advice_Adult ART Guidelines (web).pdf (accessed on 30 January 2013).
2. Cheng, V. C. *et al.*, Risk factors for development of paradoxical response during antituberculosis therapy in HIV-negative patients. *Eur. J. Clin. Microbiol. Infect. Dis.*, 2003, **22**, 597–602.
3. Meintjes, G. *et al.*, Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect. Dis.*, 2008, **8**, 516–523.
4. Bollinger, R. C. *et al.*, A randomized trial to evaluate the effectiveness of antiretroviral therapy plus HIV primary care versus HIV primary care alone to prevent the sexual transmission of HIV-1 in Serodiscordant Couples HPTN052; accessed on 7 March 2013 from http://www.hptn.org/Web%20Documents/HPTN_Protocols/HPTN052/HPTN052v1.pdf
5. Colebunders, R. *et al.*, Tuberculosis immune reconstitution inflammatory syndrome in countries with limited resources. *Int. J. Tuberc. Lung Dis.*, 2006, **10**, 946–953.
6. Burman, W. J. and Jones, B. E., Treatment of HIV-related tuberculosis in the era of effective antiretroviral therapy. *Am. J. Respir. Crit. Care Med.*, 2001, **164**, 7–12.
7. Revised NACO guidelines for ART initiation in adults. Office memorandum T-11020/36/2005 dated 4 November 2011.
8. Swaminathan, S. and Narendran, G., HIV and tuberculosis in India. *J. Biosci.*, 2008, **33**, 527–537.
9. Swaminathan, S. *et al.*, Efficacy of a 6 vs a 9-month intermittent treatment regimen in HIV-infected TB patients: a randomized clinical trial. *Am. J. Respir. Crit. Care Med.*, 2010, **181**, 743–751.
10. Swaminathan, S. *et al.*, Efficacy and safety of once-daily nevirapine- or efavirenz-based antiretroviral therapy in HIV associated tuberculosis: a randomized clinical trial. *Clin. Infect. Dis.*, 2011, **53**, 716–724.
11. Tripathy, S. *et al.*, Preliminary observations on lymphocyte subpopulation in HIV seropositive and HIV seronegative tuberculosis patients in Pune, India. *Indian J. Med. Res.*, 2000, **111**, 195–198.
12. Narita, M. *et al.*, Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am. J. Respir. Crit. Care Med.*, 1998, **158**, 157–161.
13. Tuberculosis Chemotherapy Centre. A concurrent comparison of home and sanatorium treatment of pulmonary tuberculosis in south India. *Bull. WHO*, 1959, **21**, 51–131.
14. Narendran, G. *et al.*, Comparing daily vs intermittent regimen of ATT in HIV with pulmonary tuberculosis, 2013; http://clinicaltrials.gov/ct2/show/NCT00933790?term=Daily+Vs+intermittent+ATT+in+HIV&rank=1 (accessed on 25 January 2013).
15. Breen, R. A. *et al.*, Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. *Thorax*, 2004, **59**, 704–707.
16. Kumarasamy, N. *et al.*, Incidence of immune reconstitution syndrome in HIV/tuberculosis co-infected patients after initiation of generic antiretroviral therapy in India. *J. Acquir. Immune Defic. Syndr.*, 2004, **37**, 1574–1576.
17. Lawn, S. D. *et al.*, Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. *AIDS*, 2007, **21**, 335–341.
18. Manabe, Y. C. *et al.*, Immune reconstitution inflammatory syndrome: risk factors and treatment implications. *J. Acquir. Immune Defic. Syndr.*, 2007, **46**, 456–462.
19. Narendran, G. *et al.*, Paradoxical tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS) in HIV patients with culture confirmed pulmonary tuberculosis in India and the potential role of IL-6 in prediction. *PLoS One*, 2013, **8**, e63541.
20. Lawn, S. D., Bekker, L. G. and Miller, R. F., Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. *Lancet Infect. Dis.*, 2005, **5**, 361–373.
21. Bourgarit, A. *et al.*, Explosion of tuberculin-specific Th1-responses induces immune restoration syndrome in tuberculosis and HIV co-infected patients. *AIDS*, 2006, **20**, F1–7.
22. Antonelli, L. R. V. *et al.*, Elevated frequencies of highly activated CD4 T cells in HIV patients developing immune reconstitution inflammatory syndrome. *Blood*, 2010, **116**, 3818–3827.

23. Tadokera, R. *et al.*, Hypercytokinaemia accompanies HIV-tuberculosis immune reconstitution inflammatory syndrome. *Eur. Respir. J.*, 2011, **37**, 1248–1259.
24. Sereti, I. *et al.*, Biomarkers in immune reconstitution inflammatory syndrome: signals from pathogenesis. *Curr. Opin. HIV AIDS*, 2010, **5**, 504–510.
25. Oliver, B. G. *et al.*, Mediators of innate and adaptive immune responses differentially affect immune restoration disease associated with *Mycobacterium tuberculosis* in HIV patients beginning antiretroviral therapy. *J. Infect. Dis.*, 2010, **202**, 1728–1737.
26. Zaidi, I. *et al.*, Immune reconstitution inflammatory syndrome and the influence of T regulatory cells: a cohort study in the Gambia. *PLoS One*, 2012, **7**, e39213.
27. Lawn, S. D. and Macallan, D. C., Hypercalcemia: a manifestation of immune reconstitution complicating tuberculosis in an HIV-infected person. *Clin. Infect. Dis.*, 2004, **38**, 154–155.
28. Price, P. *et al.*, Polymorphisms in cytokine genes define subpopulations of HIV-1 patients who experienced immunrestoration diseases. *AIDS*, 2002, **16**, 2043–2047.
29. Breton, G. *et al.*, Determinants of immune reconstitution inflammatory syndrome in HIV type 1-infected patients with tuberculosis after initiation of antiretroviral therapy. *Clin. Infect. Dis.*, 2004, **39**, 1709–1712.
30. Lawn, S. D. *et al.*, Urine lipoarabinomannan assay for tuberculosis screening before antiretroviral therapy diagnostic yield and association with immune reconstitution disease. *AIDS*, 2009, **23**, 1875–1880.
31. Manosuthi, W. *et al.*, Clinical case definition of paradoxical tuberculosis associated immune reconstitution inflammatory syndrome. *AIDS*, 2009, **23**, 2467–2471.
32. Wilson, I. E. *et al.*, Evaluation of paradoxical TB-associated IRIS with the use of standardized case definitions for resource limited settings. *J. Int. Assoc. Phys. AIDS Care (Chic)*, 2010, **9**, 104–108.
33. Buckingham, S. J. *et al.*, Immune reconstitution inflammatory syndrome in HIV-infected patients with mycobacterial infections starting highly active anti-retroviral therapy. *Clin. Radiol.*, 2004, **59**, 505–513.
34. Meintjes, G. *et al.*, Novel relationship between tuberculosis immune reconstitution inflammatory syndrome and antitubercular drug resistance. *Clin. Infect. Dis.*, 2009, **48**, 667–676.
35. Swaminathan, S. *et al.*, Anti-tuberculosis drug resistance tuberculosis in South India. *Int. J. Tuberc. Lung Dis.*, 2005, **9**, 896–900.
36. Gurumurthy, P. *et al.*, Decreased bioavailability of rifampicin and other antituberculosis drugs in patients with advanced human immunodeficiency virus disease. *Antimicrob. Agents Chemother.*, 2004, **48**, 4473–4475.
37. Perlman, D. C. *et al.*, The clinical pharmacokinetics rifampin and ethambutol in HIV-infected persons with tuberculosis. *Clin. Infect. Dis.*, 2005, **41**, 1638–1647.
38. Weiner, M. *et al.*, Association between acquired Rifampicin resistance and the pharmacokinetics of Rifabutin and isoniazid among patients with HIV and tuberculosis *Clin. Infect. Dis.*, 2005, **40**, 1481–1491.
39. Toman, K., What is the 'fall and rise phenomenon'. Tuberculosis case finding and chemotherapy, questions and answers, Geneva, WHO, 1979.
40. Swaminathan, S. *et al.*, Immune reconstitution syndrome following initiation of antiretroviral therapy in a patient with HIV infection and multidrug-resistant tuberculosis. *Indian J. Chest Dis. Allied Sci.*, 2005, **47**, 299–304.
41. PMDT guidelines, Central TB division, India, 2012; http://tbcindia.nic.in/pdfs/Guidelines%20for%20PMDT%20in%-20India%20-%20May%202012.pdf (accessed on March 2013).
42. Knysz, B. *et al.*, Non-Hodgkin's lymphoma as a rare manifestation of immune reconstitution disease in HIV-1 positive patients. *Postepy Hig. Med. Dosw. (Online)*, 2006, **60**, 547–551.
43. Kenali, M. S. *et al.*, Concurrent mycobacterial infection and non-Hodgkin's lymphoma at the same site in an AIDS patient. *Med. J. Malaysia*, 2004, **59**, 108–111.
44. World Health Organistaion, Consolidated ARV guidelines 2013; http://www.who.int/hiv/pub/guidelines/arv2013/art/statartadolescents/en/index.html (accessed on 30 June 2013).
45. Haddow, L. J. *et al.*, Incidence, clinical spectrum, risk factors and impact of HIV-associated immune reconstitution inflammatory syndrome in South Africa. *PLoS One*, 2012, **7**, e40623.
46. Rie, A. V. *et al.*, Xpert MTB/RIF for point-of care diagnosis of TB in high-HIV burden, resource-limited countries: hype or hope? *Expert Rev. Mol. Diagn.*, 2010, **10**, 937–946.
47. Karim, A. *et al.*, Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N. Engl. J. Med.*, 2010, **362**, 697–706.
48. Karim, A. *et al.*, Integration of antiretroviral therapy with tuberculosis treatment. *N. Engl. J. Med.*, 2011, **365**, 1492–1501.
49. Havlir, D. V. *et al.*, Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N. Engl. J. Med.*, 2011, **365**, 1482–1491.
50. Blanc, F. X. *et al.*, Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N. Engl. J. Med.*, 2011, **365**, 1471–1481.
51. Torok, M. E. *et al.*, Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)-associated tuberculous meningitis. *Clin. Infect. Dis.*, 2011, **52**, 1374–1383.
52. Meintjes, G. *et al.*, Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS*, 2010, **24**, 2381–2390.
53. Nayak, S. and Acharya, B., Deflazacort versus other glucocorticoids: a comparison. *Indian J. Dermatol.*, 2008, **53**, 167–170.
54. Brunela, A. S. *et al.*, Thalidomide for steroid-dependent immune reconstitution inflammatory syndromes during AIDS. *AIDS*, 2012, **26**, 2110–2112.
55. Arendt, G. and Nolting, T., Immune reconstitution inflammatory syndrome in HIV-positive patients: a relatively new and not fully understood phenomenon. *HIV Therapy*, 2010, **4**, 577–587.
56. Lipman *et al.*, Successful drug treatment of immune reconstitution disease with the leukotriene receptor antagonist, montelukast: a clue to pathogenesis? *AIDS*, 2007, **21**, 383–384.
57. Manosuthi, W. *et al.*, Immune reconstitution inflammatory syndrome of tuberculosis among HIV-infected patients receiving antituberculosis and antiretroviral therapy. *J. Infect.*, 2006, **53**, 357–363.
58. Worodria, W. *et al.*, Clinical spectrum, risk factors and outcome of immune reconstitution inflammatory syndrome in patients with tuberculosis-HIV coinfection. *Antivir. Ther.*, 2012, **17**, 841–848.

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 NIRT for sharing their expertise in TB–HIV management, that helped us in drafting the manuscript.