A practical approach to the diagnosis and management of paradoxical tuberculosis immune reconstitution inflammatory syndrome

TB-associated immune reconstitution inflammatory syndrome is seen after the initiation of antiretroviral therapy.

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TB-associated immune reconstitution inflammatory syndrome (TB-IRIS) is an early complication of antiretroviral therapy (ART) that occurs as a result of the rapid recovery of immune function, which drives immunopathological reactions to the antigens of *Mycobacterium tuberculosis* (MTB) present in tissue at the sites of TB disease. Two forms of TB-IRIS are recognised: paradoxical and unmasking. Paradoxical TB-IRIS occurs in patients who were started on TB treatment *before* ART who experience recurrent, new or worsening symptoms and/or clinical features of TB after staring ART. Unmasking TB-IRIS occurs in patients with undiagnosed TB who start ART and who then present with accelerated and unusual inflammatory features of TB within the first 3 months of ART.[1-3] This article will focus on paradoxical TB-IRIS with the aim of providing a practical approach to the diagnosis and management of patients presenting with suspected paradoxical TB-IRIS covering the range of possible clinical presentations.

Paradoxical TB-IRIS

Cohort studies have reported that 8 - 43% of patients starting ART while on TB treatment develop paradoxical TB-IRIS[3] and a recent meta-analysis estimated the pooled cumulative incidence as 15.7%.[4] The onset of symptoms is typically 1 - 3 weeks after ART is started, but cases can present within a few days of ART initiation and infrequently onset is delayed until after 4 weeks of treatment. Common TB-IRIS symptoms include a recurrence of night sweats, fevers, other constitutional symptoms such as malaise and symptoms related to the organ system affected. Weight loss may occur and often patients have documented fevers and a marked tachycardia. Symptoms last on average 2 - 3 months, but a minority of patients may have ongoing TB-IRIS manifestations for months or even years. In TB-IRIS cases that continue for months or years manifestations are typically tuberculous pus collections, and such patients are not usually systemically unwell for that length of time.

The diagnosis of paradoxical TB-IRIS is a clinical one, with the following 4 important components:

- the initial diagnosis of TB was microbiologically proven or based on compatible clinical and radiological features
- a clinical response to TB treatment prior to ART
- deterioration with inflammatory features of TB within the first 3 months of ART
- the exclusion of other reasons for clinical deterioration (Table I).

Paradoxical TB-IRIS occurs in patients who were started on TB treatment before ART who experience recurrent, new or worsening symptoms and/or clinical features of TB after staring ART.

Common TB-IRIS symptoms include a recurrence of night sweats, fevers, other constitutional symptoms such as malaise and symptoms related to the organ system affected.

The major risk factors identified are a low CD4 count prior to ART, shorter interval between TB treatment and ART and disseminated TB at diagnosis.[2,5] Several factors are thought to contribute to the pathogenesis of TB-IRIS: a high load of MTB infection that acts as a potent antigenic stimulus, rapid improvement in T-cell and innate immune function, high levels of pro-inflammatory cytokines and possibly inadequate immune regulatory function.[6]

Overlap of drug-resistant TB and TB-IRIS

Drug-resistant TB and paradoxical TB-IRIS are both important reasons for patients to deteriorate despite TB treatment. Drug-resistant TB is the most important alternative diagnosis to investigate when patients present with suspected TB-IRIS. In patients with TB-IRIS it is important to obtain the results of drug susceptibility testing (DST) that was performed at initial TB diagnosis, request DST on a culture isolate in the laboratory or send specimens for culture and DST if this was not done at the start of treatment. In a cohort of patients in Cape Town presenting with suspected TB-IRIS, ~10% were found to have undiagnosed rifampicin-resistant TB (MDR or rifampicin mono-resistant).[7] The two diagnoses are not, however, mutually exclusive. Patients with undiagnosed MDR-TB may partially respond to first-line TB drugs then deteriorate rapidly after ART initiation, with inflammatory features due to TB-IRIS. Such patients require an urgent DST result (with a rapid test where possible) because they deteriorate rapidly and require MDR treatment urgently. In addition, corticosteroids (see below) could potentially do harm if given to patients with sub-optimally treated TB.

Pulmonary presentations

Patients with pulmonary involvement typically present with recurrent or worsening cough that may be dry or productive. This may be accompanied by dyspnoea, chest pain, night sweats and other constitutional symptoms. Many chest X-ray patterns are described,

Table I. Case definition for paradoxical TB-IRIS[3]

There are 3 components to this case definition:

A. Antecedent requirements

Both of the 2 following requirements must be met:

1. Diagnosis of TB: the TB diagnosis was made before starting ART and this should fulfil WHO criteria for diagnosis of smear-positive PTB, smear-negative PTB or extrapulmonary TB
2. Initial response to TB treatment: the patient's condition should have stabilised or improved on appropriate TB treatment before 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 since insufficient time may have elapsed for a clinical response to be reported.)

Clinical criteria

The onset of TB-IRIS manifestations should be within 3 months of ART initiation, re-initiation, or regimen change because of 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 (found by chest X-ray, abdominal USS, CT or MRI)
3. New or worsening central nervous system TB (meningitis or focal neurological deficit – e.g. caused by 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, hepatomegaly, 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

including lobar consolidation, non-confluent or patchy infiltrates, miliary infiltrates and cavitation. If an existing infiltrate of pulmonary TB (PTB) expands after starting ART this supports the diagnosis of TB-IRIS, but in some cases new infiltrates may develop with TB-IRIS. For example, patients with a normal chest X-ray may develop a new miliary infiltrate due to TB-IRIS.

It is important to consider alternative diagnoses before making the diagnosis of TB-IRIS. An important differential diagnosis is a bacterial chest infection (pneumonia or bronchitis) and many clinicians will treat these patients with an antibiotic that covers common respiratory bacterial pathogens (e.g. oral amoxicillin or intravenous ceftriaxone if the patient is ill enough to require hospitalisation) and assess the response to the antibiotic before diagnosing TB-IRIS. In patients who have features of sepsis syndrome a blood culture should be performed. If the TB DST result is not known this should be requested on a culture isolate present in the laboratory or a fresh sputum sample.

In patients who present with respiratory distress and bilateral ground glass infiltrate *Pneumocystis* pneumonia (PCP) should be considered. Investigations in such cases should include an arterial blood gas and induced sputum for PCP direct fluorescence antigen test or PCP PCR, if available. Other diagnoses to consider are pulmonary Kaposi's sarcoma (examine mouth and skin carefully for lesions) and pulmonary cryptococcosis (investigated with a serum cryptococcal antigen test). It is particularly important to consider alternative diagnoses in patients in whom the TB diagnosis was not initially microbiologically proven who were started on treatment for smear-negative PTB.

The diagnosis of paradoxical TB-IRIS is a clinical one.

Enlarging lymph nodes

Enlarging lymph nodes are a common feature of paradoxical TB-IRIS. This may or may not be accompanied by constitutional symptoms and TB-IRIS features involving other organ systems. Cervical nodes are most frequently affected, but axillary, inguinal, thoracic and abdominal nodes may also be affected. When peripheral nodes are involved there are frequently more features of acute inflammation than would usually be expected with TB lymphadenopathy in patients not on ART: tense, red overlying skin and marked tenderness on palpation (Fig. 1). Such TB-IRIS lymphadenitis may be misdiagnosed as a bacterial abscess. Thoracic node enlargement may be complicated by airway compression or superior vena cava syndrome, retroperitoneal node enlargement may be complicated by ureteric obstruction and retroperitoneal or inguinal node enlargement may be complicated by deep-vein thrombosis due to compression of the inferior vena cava, iliac or deep femoral veins.

TB-IRIS lymph nodes are initially firm, but typically suppurate and become fluctuant within a few weeks. An aspirate taken of the tuberculous pus from these nodes is often AFB-positive and may or may not

Fig. 1. ***Cervical lymph node enlargement due to TB-IRIS****. The lymphadenitis often results in red, warm overlying skin and is frequently tender to palpation. The nodes often suppurate to form tuberculous abscesses. Large volumes of tuberculous pus were repeatedly aspirated from this patient's lymph nodes.*

be TB culture-positive. It is important to request DST on aspirates to exclude MDR-TB. Other differential diagnoses include lymphoma and Kaposi's sarcoma (KS), particularly if the nodes remain firm and do not suppurate (Fig. 2). If the diagnosis of TB was not initially proven it is important to perform a needle aspirate for AFB staining and microscopy and if AFB-negative and the lymph nodes do not suppurate an excision biopsy is indicated. Suppuration makes lymphoma and KS very unlikely.

Repeated aspirations with a wide-bore needle of tense, enlarged nodes can provide symptomatic relief and cosmetic improvement. A wide-bore needle is required because the pus is often thick. These collections are often multi-loculated and require passes of the needle in different

Fig. 2. ***Kaposi's sarcoma lymph node involvement mimicking TB-IRIS****. A 24-year-old HIV-infected man with a CD4 count of 211 was diagnosed with TB pericardial effusion and was started on TB treatment and prednisone. TB symptoms resolved and he gained 8 kg in weight. Eight weeks after starting TB treatment he commenced ART. Four weeks into ART he developed swallowing difficulties and was found to have enlarged tonsils with extensive lymphadenopathy (1 - 3 cm in size and firm) in the cervical, axillary and inguinal regions. He also had subcutaneous occipital swellings. He had no mucosal or skin KS lesions (a). The lymphadenopathy was initially thought to be caused by TB-IRIS, but there was a concern that the involvement of so many lymph node regions, tonsils and the subcutaneous lesions were unusual for TB-IRIS. An excision biopsy of a lymph node was thus performed and demonstrated Kaposi's sarcoma (b).*

planes. Care should be taken to avoid large vessels of the neck when aspirations are performed. We advise against incision and drainage of such nodes when they suppurate because this often results in persistent draining sinuses.

Tuberculous abscesses

Tuberculous abscesses may develop from suppurative lymphadenitis or may arise *de novo*. The most common form is a psoas abscess, often bilateral in TB-IRIS. Subcutaneous abscesses, commonly on the chest wall, may also occur. Aspiration of superficial abscesses with a wide-bore needle may provide symptomatic relief and pus should be sent for culture and DST to exclude MDR. Large psoas abscesses can be aspirated under ultrasound guidance to exclude MDR.

Central nervous system involvement

Paradoxical TB-IRIS can cause enlarging intracerebral tuberculomas or tubercular abscesses, meningitis or myeloradiculitis. These manifestations can recur after starting ART or may manifest for the first time in a patient who was not known to have neurological TB prior to ART. In a study conducted in Cape Town,[8] 12% of TB-IRIS patients assessed at a referral hospital had CNS manifestations. Neurological TB-IRIS is associated with the highest mortality risk (Fig. 3). In the same Cape Town study, 13% of patients died and 17% were lost to follow-up (presumed to have died). A substantial proportion of patients are left with long-term disability after an episode of neurological TB-IRIS.

It is possible that adjunctive corticosteroid treatment in HIV-infected patients with TB meningitis continued through the period of early ART may reduce the incidence or severity of paradoxical TB meningitis-IRIS. However, this has not been studied and it is important to note that paradoxical TBM-IRIS may develop even in patients on high-dose prednisone.[9] Patients presenting with TB meningitis-IRIS may have either polymorph or lymphocyte predominance in the CSF and some patients have a very high CSF protein. It is important to exclude cryptococcal meningitis with a CSF cryptococcal antigen test or culture. DST results from the initial TB episode should be followed up.

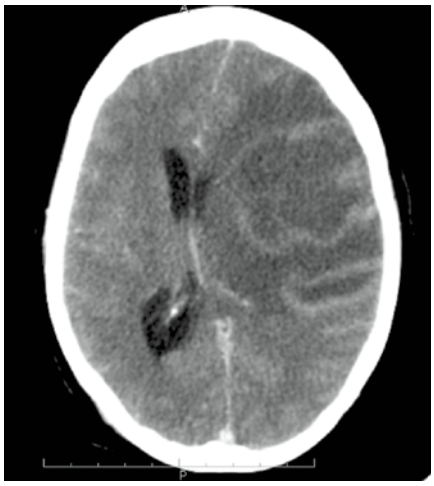

Fig. 3. ***Fatal enlargement of intracerebral tuberculoma due to TB-IRIS.*** *A 34-year-old HIV-infected woman with a CD4 count of 26 was diagnosed with TB meningitis after presenting with headaches and neck stiffness. Lumbar puncture demonstrated lymphocytic meningitis, CSF cryptococcal antigen test was negative and chest X-ray was compatible with pulmonary TB. She started TB treatment and prednisone and significantly improved. She was able to self-care after discharge and started ART 6 weeks after TB treatment. Two weeks after starting ART she was admitted following several generalised convulsions and had a depressed level of consciousness and right hemiparesis. CT scan showed a large left fronto-parietal ring-enhancing lesion with extensive surrounding oedema and mid-line shift. ART was stopped, she was commenced on high-dose dexamethasone and anticonvulsants, but she deteriorated and died 2 days later.*

Drug-resistant TB and paradoxical TB-IRIS are both important reasons for patients to deteriorate despite TB treatment.
Hepatic TB-IRIS is probably more common than is appreciated clinically.

In patients presenting with enlarging intracerebral tuberculomas or tubercular abscesses the important differential diagnoses to consider are cerebral toxoplasmosis, cryptococcoma, lymphoma, bacterial abscess and MDR TB. The investigation of such patients will depend on the individual case. If the patient was diagnosed with disseminated TB and tuberculoma prior to ART and the tuberculoma was responding to TB treatment, but then enlarges on ART, further investigation is probably not required. In other cases it may not be clear whether the enlarging brain lesion is a tuberculoma enlarging due to IRIS or due to one of the

differential diagnoses. Investigations such as serum toxoplasmosis IgG (a positive test reflects latent toxoplasmosis infection and does not confirm cerebral toxoplasmosis, but a negative test makes cerebral toxoplasmosis very unlikely), serum cryptococcal antigen test and even brain biopsy may be indicated. Empiric toxoplasmosis treatment may be considered in such cases.

Myeloradiculitis is an infrequent TB-IRIS manifestation characterised by tuberculous inflammation around the lower spinal cord and lumbosacral nerve roots resulting in flaccid paraparesis. The CSF shows pleocytosis, often with a very high protein level and spinal MRI shows characteristic features.

Enlarging effusions (pleural and pericardial effusions and ascites)

Paradoxical TB-IRIS may present with enlargement or recurrence of TB serous effusions diagnosed before ART or new effusions that emerge on ART. Breathlessness due to large pleural effusions may be relieved by aspiration of up to 1.5 litres of fluid. Enlargement of pericardial effusions due to TB-IRIS can be rapid, resulting in life-threatening cardiac tamponade requiring urgent pericardiocentesis. Paracentesis of ascites can provide symptomatic relief. Chylous ascites and chylothorax due to TB-IRIS are described.

It is again important to consider alternative diagnoses. Examples are bacterial empyema (Gram stain and bacterial culture should be performed, particularly if the aspirate is cloudy or purulent) and Kaposi's sarcoma (especially if effusion is bloody). It is also important to exclude drug-resistant TB by sending the aspirate for TB culture and DST. Effusions usually respond well to corticosteroids which may prevent re-accumulation.

Liver involvement

Hepatic TB-IRIS is probably more common than is appreciated clinically. Haematogenous dissemination of TB is common in advanced HIV. Thus, when such patients develop TB-IRIS liver involvement is common. We have reported that 56% of patients with TB-IRIS have clinical hepatomegaly.[7] The hepatomegaly in TB-IRIS is frequently tender and patients may have symptoms of right upper quadrant pain, nausea and vomiting. Many of these patients have multisystem involvement, but in some patients the presentation is dominated by the hepatic features. In a case series of patients with hepatic TB-IRIS the clinical presentation in all of these patients was characterised by hepatomegaly and an abnormal liver profile, while two-thirds had a fever.[10] The median duration of ART prior to presentation was 30 days. This is longer than previously noted in TB-IRIS and is probably due to the fact that the majority of these patients do not become overtly jaundiced and that their mode of presentation (hepatomegaly) is noted later than a pulmonary or neurological presentation. The typical pattern of liver enzyme abnormality is a mixed picture with moderate elevation of transaminases but a far more significant rise in the canalicular enzymes. Gamma glutamyl transpeptidase (GGT) is significantly more elevated in TB-IRIS patients when compared with HIV-negative patients with TB involving the liver. While serum bilirubin may increase, clinical jaundice is less common.

Hepatic TB-IRIS is probably more common than is appreciated clinically.

A clinical conundrum for many clinicians is differentiating hepatic TB-IRIS from a TB drug, ART or co-trimoxazole drug-induced liver injury (DILI).[11] Unfortunately there are no features absolutely predictive of either an IRIS or a DILI. Tender hepatomegaly, the preponderance of an elevation in the canalicular enzymes, the absence of jaundice, maintained synthetic liver function and IRIS features in another organ system (e.g. pulmonary) may be pointers towards a TB-IRIS rather than a DILI. The more definitive diagnostic route is to perform a liver biopsy. However, this procedure is invasive and not readily available. Histological features observed in patients with TB-IRIS include significantly increased numbers of granulomas per liver core with abundant eosinophils palisading around these granulomas (Fig. 4).

Less common presentations

Splenic involvement may result in enlargement, formation of abscesses in the spleen and cases of splenic rupture are described. Inflammation of the peritoneal surface may give rise to peritonitis with clinical examination findings suggesting a 'surgical abdomen'. Intestinal involvement may be complicated by ileocaecal perforation. Other rare features that are described include arthritis, osteitis, parotitis and epididymo-orchitis.

Corticosteroids

Corticosteroid adjunctive therapy has been used in TB outside the context of IRIS to treat TB pericarditis, TB meningitis and pulmonary or miliary TB complicated by respiratory failure. There is evidence that corticosteroids reduce mortality in TB meningitis. Soon after TB-IRIS was first recognised, corticosteroids were used to treat severe cases with anecdotal benefit. However, there are potential risks in patients with advanced HIV because of the immunosuppressive properties of corticosteroids. These risks include development or acceleration of KS or precipitation of other infections, such as herpes virus reactivations.

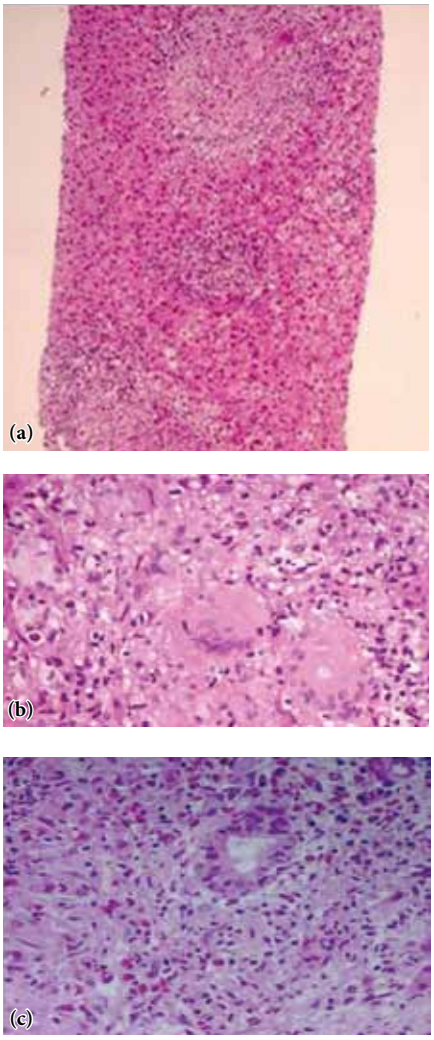

Fig. 4 Hepatic TB-IRIS. *A 24-year-old HIV-infected man, CD4=79, presented with features compatible with disseminated TB (nodular pulmonary infiltrate, splenic micro-abscesses, constitutional symptoms). His sputum was negative for AFBs on direct staining but subsequently cultured drug-sensitive MTB. He was commenced on 4-drug TB treatment. Liver enzymes done at the time were as follows: TBr 10, ALP 183, GGT 215, ALT 68 AST 109 and were attributed to TB involvement of the liver and possible drug-adaptive effects of the TB medication. Two months into TB therapy ART was started (stavudine, lamivudine and efavirenz). Approximately 3 weeks after starting ART, he presented with right upper quadrant discomfort, nausea and recurrence of night sweats and fever. Clinically he had a palpable mildly tender hepatomegaly. The liver enzyme profile revealed TBr 28, ALP 1081, GGT 1468 ALT 108 AST 163. A liver biopsy demonstrated multiple non-caseating granulomata with a mixed inflammatory cell infiltrate. The patient's ART and TB therapy was continued. His liver profile settled over the ensuing 6 months and he continues to do well with a suppressed HIV viral load and CD4 of >500. (a) Low-power H&E – core of liver demonstrating numerous non-caseating granulomas; (b) high-power H&E – coalescing multinucleate Langhans giant cells forming granulomas; (c) high-power H&E – abundant eosinophils in a mixed inflammatory cell infiltrate.*

A randomised placebo-controlled trial of prednisone was conducted in Cape Town.[12] Patients received prednisone (or identical placebo) 1.5 mg/kg/d for 2 weeks followed by 0.75 mg/kg/d for 2 weeks; treatment was then stopped. Patients with immediately life-threatening TB-IRIS (e.g. neurological involvement) were excluded from this study. Prednisone resulted in significant reduction in days of hospitalisation and outpatient therapeutic procedures and also more rapid symptom and radiological improvement and C-reactive protein reduction. No mortality benefit was demonstrated, but those with life-threatening IRIS were excluded. There was no excess of metabolic side-effects or severe infections with this 4-week course. About one-fifth of patients who responded to prednisone had symptom relapse after stopping the 4-week course. Thus, for a subgroup of TB-IRIS patients longer durations of corticosteroids may be required to control TB-IRIS symptoms, but the requirement for longer durations of prednisone needs to be assessed on an individual basis.

In the individual case of TB-IRIS the decision whether to treat with corticosteroids needs to weigh several considerations. The severity of symptoms and the organ system involved are important considerations. The trial described above showed that corticosteroids provide symptom benefit and reduce health care utilisation, fairly modest benefit for a condition that is self-limiting. However, in patients with neurological TB-IRIS, where mortality is substantial, corticosteroids may provide survival benefit, but this has not been and probably will not be tested in a controlled trial. Nonetheless, most clinicians would regard neurological TB-IRIS as a strong indication for corticosteroids. On the other hand, in many cases of TB-IRIS the clinician is not initially confident of the diagnosis until investigations exclude alternative diagnoses or, in the case of patients with pulmonary presentations, the patient fails to respond to treatment for a bacterial infection. In such cases it is prudent to defer corticosteroids until the diagnosis is more certain. In particular, where MDR TB is suspected, steroids may be deferred until DST results are available. The potential complications of corticosteroids also need to be considered. For example, corticosteroids should be avoided in patients with KS because of the risk of exacerbating the KS.

Other treatments

Non-steroidal anti-inflammatory drugs (NSAIDs) have also been used in the treatment of TB-IRIS and it has been suggested that TNF-alpha blockers and thalidomide may have a role in the treatment of refractory tuberculomas that may occur with TB-IRIS. Aspiration of pus collections may provide symptom benefit, as described above. Other supportive treatments depend on the organ system involved. In most cases ART can be continued, but in certain life-threatening situations (e.g. neurological involvement with depressed level of consciousness) many clinicians would temporarily interrupt ART.

TB-IRIS is generally not an indication for prolonging TB treatment, but in patients who develop chronic tuberculous abscesses due to TB-IRIS consideration should be given to prolonging TB treatment until after these collections have resolved or for 6 months following the last positive TB culture on an aspirate from the collection. It is our experience that these collections may remain positive with drug-susceptible MTB for several months, presumably because of poor drug penetration.

References available at www.cmej.org.za

IN A NUTSHELL

- Paradoxical TB-IRIS occurs in roughly 1 in 6 HIV-TB patients starting ART.
- Paradoxical TB-IRIS does not mean TB treatment is failing.
- It occurs due to an immunopathological reaction to TB antigens causing inflammation at sites of TB disease.
- Patients present with recurrent, new or worsening features of TB usually within the first 4 weeks of ART.
- The most common features are recurrent symptoms, fevers, enlarging TB lymph nodes and worsening pulmonary TB.
- It is rarely life-threatening, the major exception being when the central nervous system is involved (e.g. meningitis and tuberculoma).
- It is important to exclude drug-resistant TB in all patients presenting with paradoxical TB-IRIS.
- Consider other differential diagnoses relevant to the specific clinical presentation (e.g. bacterial/fungal infection or drug reaction).
- Hepatic TB-IRIS presents with an enlarged tender liver and predominantly cholestatic abnormalities of liver function tests.
- Corticosteroids provide symptom benefit and reduce morbidity. Use when alternative diagnoses are excluded. Steroids may be particularly important in patients with neurological TB-IRIS.

SINGLE SUTURE

Wake up after surgery with Ritalin

Anaesthetics leave people groggy, but a dose of Ritalin could wake them up. Anaesthetised rats injected with the drug awoke almost immediately, suggesting that the drug could be used to reverse the effects of general anaesthesia.

Currently there is no way to reverse anaesthesia. 'We just sit and let the drugs wear off,' says Emery Brown of Massachusetts General Hospital in Boston.

Since general anaesthetics seem to suppress the firing of neurons in the brain's cortex, Brown's team reasoned that boosting their activity might have the opposite effect. Ritalin increases the levels of dopamine in the brain's arousal pathways. The anaesthetised rats given the drug came to in an average of 90 seconds, compared with 280 seconds when left to wake up naturally.

If replicated in humans, Ritalin could enable patients to feel wide awake in minutes, rather than hours. Similar drugs are being investigated to help rouse people from coma.

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