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REVIEW ARTICLE

Tuberculosis immune reconstitution inflammatory syndrome in countries with limited resources

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SUMMARY

Mycobacterium tuberculosis **infection accounts for probably one third of human immunodeficiency virus (HIV) related immune reconstitution inflammatory syndrome (IRIS) events, particularly in developing countries where HIV and tuberculosis (TB) co-infection is very common. Small cohort studies of HIV-positive patients with active TB treated with antiretroviral therapy (ART) suggest an incidence of TB IRIS varying between 11% and 45%. Risk factors for TB IRIS that have been suggested in certain studies but not in others include: starting ART within 6 weeks of starting TB treatment; extra-pulmonary or disseminated disease; a low CD4+ lymphocyte count and a high viral load at the start of ART; and a good immunological and virological response during highly active antiretroviral therapy (HAART). It is important to agree on a clinical case definition of TB IRIS that could be used in resource-limited settings. Such a case definition could be used to determine the exact incidence and consequences of TB IRIS and would be valuable worldwide in clinical trials that are needed to answer questions on how this phenomenon could be prevented and treated.**

KEY WORDS: HIV infection; *Mycobacterium tuberculosis*; antiretroviral treatment; immune reconstitution inflammatory syndrome

SINCE the use of antiretroviral therapy (ART), immune reconstitution inflammatory syndrome (IRIS) has been described in association with many concomitant infections such as mycobacterial infections (*Mycobacterium tuberculosis*, *M. xenopi*, *M. kansasii*, *M. avium complex*, leprosy), fungal infections (cryptococcal and *Pneumocystis jirovecii* infection) and viral infections (herpes simplex, herpes zoster, cytomegalovirus, progressive multifocal encephalopathy and hepatitis B infection).[1,2] IRIS associated with leishmania infection, Reiter's syndrome, Guillain Barré and several dermatological conditions have occasionally been reported.[1] Other manifestations not clearly related to infectious agents have also been described, such as Graves disease,[3–5] sarcoidosis and other autoimmune disorders.[6–8] Lastly, malignancies such as Kaposi's sarcoma and lymphoma have also been seen in the framework of IRIS.[9–11]

Other terms used instead of IRIS are immune restoration disease and paradoxical reaction. While the term IRIS is almost solely used in human immunodeficiency virus (HIV) seropositive patients who initiated ART, the term paradoxical reaction is generally used to describe a clinical worsening of tuberculosis (TB) disease (in both HIV-seronegative and -seropositive patients) after the initiation of anti-tuberculosis treatment.

TB without HIV infection also may lead to cellular immune suppression,[12] which is reversible with anti-tuberculosis treatment. The pathogenesis of paradoxical reactions in HIV-seronegative TB patients might be explained by an increased immunological response of reactive lymphocytes and monocytes.[13] In the case of IRIS, the increased immunological response is enhanced not only by TB treatment, but potentially also by the reduction in the viral load due to ART, leading to a partial immune reconstitution. IRIS may also occur as a clinical worsening of a previously present but clinically unapparent disease (the 'unmasking type' of IRIS).[14,15] In this paper we review what is known and unknown about TB IRIS, and discuss ways to diagnose and manage this condition.

WHAT IS KNOWN ABOUT TB IRIS?

Incidence of TB IRIS and its risk factors

Paradoxical worsening of TB after initiation of anti-tuberculosis treatment has been reported in about 2–23%[12,13] of treated TB patients without HIV infec-

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tion; it occurs more frequently in patients with extrapulmonary and disseminated TB.[13] In HIV-seronegative patients with paradoxical reactions, there was a lower baseline absolute lymphocyte count, and a greater increase in lymphocytes during a paradoxical response.[13]

In patients taking ART, IRIS against TB antigens probably account for one third of all HIV-related IRIS events,[16] particularly in developing countries where HIV and TB co-infection is very common. Studies performed in Europe and the USA reported an incidence of TB IRIS varying between 11%[17] and 45%.[18–24] Paradoxical reactions were reported by Narita et al. to occur in 12/33 (36%) HIV-seropositive patients with active TB receiving ART, compared to 7% of cases not receiving ART and 2% of cases who were not HIV infected.[20] In a study performed in India, 11 of 144 HIV individuals with active TB followed for 72 person-years developed IRIS within 6 months of initiating highly active antiretroviral therapy (HAART) (incidence of IRIS 15.2 cases per 100 patient-years).[25] In another study in India, a total of 126 patients received anti-tuberculosis treatment and HAART.[26] IRIS, defined as a transient worsening or exacerbation of symptoms and lesions during therapy documented by clinical examination and radiological investigations, was seen more often in patients with active TB than in those without active TB at the start of HAART (11 [8.73] vs. 3 [2.32%], $P = 0.05$). We have found no data describing the incidence of TB IRIS in Africa.

The following risk factors for TB IRIS have been identified: starting ART within the first 2 months of TB treatment[21] and extra-pulmonary or disseminated disease. Other potential risk factors are a low $CD4^+$ lymphocyte count (<50 cells/μl at the start of ART), a viral load of $>10^5$ $\log_{10}$ copies/ml, a good immunological response (rise in $CD4^+$ lymphocyte count percentage) and a virological response (decreasing viral load) during HAART.[20,22,23,27,28] Kumarasamy et al., however, found that there was no statistical difference in $CD4^+$ lymphocyte count rise, $CD4^+$ lymphocyte count at the start of HAART and duration of TB treatment at HAART initiation between those who did and those who did not develop IRIS.[25] The risk of IRIS may be related to the bacillary burden and it may therefore be observed more often in patients with a very low $CD4^+$ lymphocyte count because such patients may have a higher bacillary burden.[28] The load of antigen could be responsible for the over-vigorous inflammatory response of a recovering immune system. This would result in clinical IRIS events. The study by Narita et al., however, suggested that the onset of IRIS was more temporally related to the start of ART (15 ± 11 days) than to the start of TB treatment (109 ± 72 days, $P < 0.001$).[20]

Pathogenesis of TB IRIS

The pathogenesis of IRIS in general and TB IRIS in particular remains poorly understood. It is generally thought to be the restoration of the immune responses to antigens (viable or not) producing exuberant inflammatory reactions. Given the fact that shortly after the initiation of HAART there is a rapid recirculation of memory cells,[29] these memory cells may play a role in the development of IRIS. Such reactions do not require the presence of viable organisms because they can occur after successful TB treatment. Acid-fast bacilli (AFB) identified in IRIS events are often not found to be viable. In certain TB IRIS patients, rapid restoration of the cutaneous tuberculin reaction has been observed.[20,30] An increase in interleukin (IL) 6, soluble IL-6 receptor and activation markers ($CD38^+$) has also been reported.[1] The immunopathogenic mechanisms causing IRIS seem to be determined by the pathogen. For example, mycobacterial IRIS is associated with delayed-type hypersensitivity (DTH) responses to mycobacterial antigens, whereas there is evidence of a CD8 T-cell response in herpes virus IRIS.[1] Furthermore, the association of different cytokine gene polymorphisms with mycobacterial or herpes virus IRIS provides evidence for differences in pathogenic mechanisms as well as in genetic susceptibility to IRIS.[1] For example, the cytokines genes TNFA-308*2 and IL6-174*G were not associated with herpes virus IRIS but with mycobacterial IRIS.[1]

On the other hand, the lack of a specific immune response to a particular antigen leading to an abnormal reaction of the immune system has also been suggested as a possible pathophysiological mechanism of IRIS. In a study of 11 patients with TB IRIS in the United Kingdom, it was suggested that TB IRIS may be associated with inadequate immune reconstitution rather than vigorous specific T-cell responses. In these patients, the concomitant administration of IL-2 and GM-CSF immunotherapy with effective ART was clinically beneficial.[31]

In certain patients, the immunopathogenesis of IRIS may be related to the formation of granuloma. Two cases of IRIS accompanied by hypercalcemia have been reported, one associated with cryptococcosis and the other with TB.[32,33] Hypercalcaemia is a recognised manifestation of other granulomatous lung diseases, including sarcoidosis, TB and fungal infections. The formation of granulomas, however, can not be the explanation for IRIS observed in patients with diseases that have no granulomatous pathogenesis, such as viral infections.

Clinical features of TB IRIS

As already stated above, TB IRIS may be diagnosed in two situations. In the first, the TB is unrecognised at the moment HAART is started, the 'unmasking' type of IRIS. During HAART, the diagnosis of TB becomes evident because, for example, the patient develops AFB-containing abscesses. In the second, a known TB patient on successful TB treatment develops a worsening of the clinical picture after the introduction of HAART.

The interval between the start of HAART and the onset of TB IRIS is variable, but ranges from less than 1 week to several months. In the majority of patients, the TB IRIS occurs within the first 4–8 weeks of ART. In the study by Kumarasamy et al., the median time to development of clinical IRIS was 42 days (range 10–89).[25] Several studies from Europe and North America have suggested shorter median times of 11–14 days.[15,16] One case of TB IRIS occurring one year[34] and another case about 2 years after initiation of HAART have been described.[35] We observed a patient who developed a second TB IRIS episode (when the $CD4^+$ lymphocyte count had increased to 300 cells/μl) 4 years after a first episode of TB IRIS (when the $CD4^+$ lymphocyte count was <50 cells/μl) (R Colebunders, unpublished data). It is important for clinicians to appreciate that IRIS events may happen following the immune restoration produced by first-line ART, but also during any subsequent periods of immune restoration, for example in patients failing first-line ART who are switched to an effective second line regimen or a structured (or unstructured) treatment interruption (L John, personal communication).

A patient with TB IRIS generally presents with fever. Other clinical manifestations depend on the site of the TB. The time course of IRIS events may be considerably more acute than one would usually expect with TB: patients may present acutely unwell within a week or two of starting ART. In the case of pulmonary TB, the patient may start to complain of increased cough and dyspnoea after the start of HAART. Stridor[17,36] and severe respiratory failure has been described.[37] Radiologically, increased pulmonary infiltrates,[18,20,21,36,38] pleural effusions[20,36,39,40] and mediastinal lymphadenopathy,[20,25,36,38,41,42] sometimes with tracheal compression, can be seen. Peripheral lymph nodes often enlarge or appear and may become fluctuant.[18,20,25,38,40,41,43,44] Patients may develop skin lesions,[18,20,45] subcutaneous abscesses or muscle abscesses in the framework of IRIS. Abdominal presentations may include enlarged lymph nodes, which may cause compression of vessels or the urethra, and even thrombo-embolic events.[18] In the case of intestinal TB, patients may develop a bowel perforation.[34] Abscesses may also develop in the liver and spleen.[18,39] Peritonitis with or without ascites has also been reported.[20,40] Abscess formation may occur in the central nervous system (CNS) with symptoms of headache, fever and TB choroidal nodules on ophthalmic examination.[46,47] Less frequently reported findings are tenosynovitis,[43] arthritis, parotitis and osteomyelitis.[18] Last, a case of enlargement of the testicles and epididymis has been reported.[39]

Diagnosis of TB IRIS

IRIS is mainly a clinical diagnosis. Particularly when IRIS develops shortly after the start of anti-tuberculosis treatment and ART, laboratory tests may not be useful to differentiate between TB IRIS and anti-tuberculosis treatment failure. They might, however, help in distinguishing it from other infections or diseases or from drug toxicity.

A rise in $CD4^+$ lymphocyte count and a decrease in viral load are common findings associated with TB IRIS, but cases of IRIS without a significant increase in $CD4^+$ lymphocyte count have been observed.

French et al. have proposed a definition for IRIS,[1] but as it requires viral load or, in the absence of viral load, a $CD4^+$ lymphocyte count as well as measurement of DTH response to mycobacterial antigens, this definition is not useful in resource-poor settings.

A rapid recovery of tuberculin reactivity in TB IRIS (86% of subjects converting to tuberculin positivity after 8 weeks of HAART) was observed in a small series of patients, in marked contrast to the minimal and delayed recovery of responses noted in other acquired immune-deficiency syndrome (AIDS) patients.[20]

Differential diagnosis of TB IRIS

The differential diagnosis of TB IRIS includes side effects of ART (e.g., drug fevers), TB infection not responding to treatment due to resistance or poor adherence to treatment, and other HIV or non-HIV related infections. In the case of late IRIS, ART failure has to be excluded.

Management of TB IRIS

For the moment there are no evidence-based guidelines for the treatment or prevention of TB IRIS. To reduce the incidence of TB IRIS, it has been suggested to reduce the bacillary load sufficiently prior to the start of HAART by respecting a lengthy enough interval between the start of anti-tuberculosis treatment and HAART. However, the ideal interval between the start of anti-tuberculosis treatment and the introduction of HAART is not yet known.

When TB IRIS occurs, anti-tuberculosis treatment should be continued or started. Corticosteroids at a dose of 20–40 mg/day[20,25,39,48] for 2–4 weeks may be helpful in the presence of persistent fever, abscesses, dyspnoea or meningitis. Whether non-steroidal anti-inflammatory drugs (NSAIDs) may also be of help should be investigated. Large abscesses should probably be drained, but how often this should be done is unknown. In the case of life-threatening forms of TB IRIS, such as tuberculous meningitis with increased intracranial pressure due to IRIS, stopping ART temporarily could be considered. However, this is generally not necessary. So far, TB IRIS events do not seem to be fatal if health staff recognise the condition early, and patients can therefore be clinically managed at district hospital level.

WHAT NEEDS TO BE KNOWN ABOUT TB IRIS?

First, we have to agree on a clinical case definition of TB IRIS that could be used in resource-constrained

settings. We propose initially to use a relatively broad definition of TB IRIS to study all possible aspects of this phenomenon. Such a case definition will need to be validated in prospective studies.

Using such a case definition, data on the incidence of TB IRIS in countries with high prevalence of HIV-TB co-infection need to be collected. We also need more information on potential mortality and morbidity associated with TB IRIS, including possible sequelae such as blindness as a possible consequence of IRIS in patients with TB CNS infections. Risk factors and predictors for TB IRIS need to be identified.

We have to better understand the pathophysiology of both early and late forms of TB IRIS and to identify possible immunological markers that could help to predict and/or diagnose TB IRIS. Possible immunopathophysiological mechanisms that should be investigated include: 1) an unbalanced inflammatory response against *M. tuberculosis* as a result of a disproportionate *M. tuberculosis*-specific response of reconstituted effector T cells, and/or impaired reconstitution of anti-inflammatory regulatory T cells; and 2) an excessive activation of monocytes/macrophages due to their functional recovery in the absence of TB containment by $CD4^+$ T cells. The value of repeating tuberculin skin testing (TST) to diagnose TB IRIS also needs further evaluation. We also need to determine the role of the mycobacterial load as a risk factor for IRIS and whether TB chemoprophylaxis in 'IRIS high-risk' individuals could reduce the incidence of TB IRIS.

To scale up the roll-out of HAART, we will need to decentralise HIV treatment to the level of health centres. We therefore need to know how to diagnose TB IRIS clinically at the primary health care level, and when a health care worker at this level should refer a patient or call for advice for suspicion of IRIS.

Important questions concerning the management and prevention of TB IRIS need to be answered, including: 1) when is the optimal moment HAART should be started in an HIV-seropositive patient who has initiated anti-tuberculosis treatment? 2) How should TB IRIS events be safely managed? 3) Should the management of early and late TB IRIS be different? and finally, 4) How can the development of TB IRIS be prevented?

WHAT HAS TO BE DONE TO FILL THE KNOWLEDGE GAP?

To fill the knowledge gap about TB IRIS, the results of the following studies are needed.

Cohort studies

Cohorts of patients with known TB and patients without evidence of active TB started on HAART should be established. In both populations, the incidence of TB IRIS should be determined and the characteristics of these patients described.

Randomised clinical trials

With a better idea about the incidence of TB IRIS (based on results of cohort studies), clinical trials should be performed comparing early vs. late ART in TB patients under TB treatment (Table). Such a trial is currently planned by the Special Programme for Research and Training in Tropical Diseases (TDR) and the European and Developing Countries Clinical Trials Partnership Programme (EDCTP) in several sites in Tanzania and Uganda. In this study, HIV-seropositive patients with active TB and a $CD4^+$ lymphocyte count between 200 and 500 cells/μl will be treated with short-course anti-tuberculosis treatment, either together with HAART or followed by HAART at the end of the TB treatment. In the PART (Punctuated Anti-Retroviral Treatment) study recently started in Uganda, HIV-seropositive patients with active TB and a $CD4^+$ lymphocyte count of 350 cells/μl are enrolled. In one arm, patients will receive a triple nucleoside reverse transcriptase inhibitor regimen during the course of TB treatment; the other arm will only receive TB treatment. Both trials may provide information about incidence of IRIS in HIV-TB co-infected patients with a relatively high $CD4^+$ lymphocyte count.

Trials of early vs. late ART in HIV-positive patients with active TB, but with a $CD4^+$ lymphocyte count <200 cells/μl (patients most at risk for TB IRIS), should also be performed. Other trials that should be considered include trials to determine the added value of TB preventive treatment in HIV-positive patients while on ART and before ART is started. The role of corticosteroids, NSAIDs and thalidomide in the prevention and treatment of TB IRIS should be investigated. Trials should also compare the role of stopping or continuing HAART in patients developing TB IRIS.

WHAT TO DO IN THE MEANTIME?

It is important to agree on a provisional clinical case definition of TB IRIS that can be used in resource-limited settings.

Suggested definition of TB IRIS for use in countries with limited resources

1 TB-treated patient, at the start of HAART:
   i A suspected TB IRIS case can be defined as a patient who meets the following three criteria:
      - An initial clinical response to TB treatment, based on a combination of some of the following factors: cessation of fever, relief of pulmonary symptoms, decrease in lymph node size, termination of meningeal signs (depending on presenting symptoms)

Table Randomised clinical trials planned or in progress comparing early vs. deferred HAART in patients with HIV-TB co-infection

Study (sponsor)	Description	Status of the study
1 Trial in India (Indian National AIDS Control Organization)	HIV-TB co-infected patients with a CD4+ lymphocyte count <250 cells/μl will be randomised to start a once-daily regimen of ddI, 3TC, EFV or NVP, 2 months after the start of TB treatment.	Started March 2006
2 PART study, Uganda (NIAID)	HIV-infected patients with culture-positive TB and a CD4+ lymphocyte count >350 cells/μl are randomly assigned to receive 6 months of ARV (ABC, ZDV, 3TC) or to delay ART until CD4+ lymphocyte count drops below 200 cells/μl.	Recruitment started in 2005
3 Study in Uganda, Tanzania (EDCTP/TDR)	Double-blind, placebo-controlled, randomised trial, two treatment arms (900 patients per arm): Group 1: SCC plus HAART (as soon as SCC is tolerated) for 6 months, followed by HAART Group 2: SCC plus placebo for 6 months, followed by HAART All SCC regimens contain rifampicin throughout the 6 months. EFV is the NNRTI drug of choice unless otherwise specified in the protocol A sub-study on the bioavailability of the fixed-dose formulation Rifafour containing isoniazid, rifampicin, pyrazinamide, ethambutol and the WHO-recommended first-line ARV drugs zidovudine, lamivudine, efavirenz administered to new TB patients at different levels of immunosuppression	To start in 2006 Sub-study started November 2005
4 CAMELIA trial, Cambodia (ANRS, NIH)	Two-arm comparative trial of the efficacy of early (2 weeks) vs. late (8 weeks) initiation of ART, 600 patients enrolled in two sites. EFV is given at 600 mg	Study started January 2006
5 Start study, South-Africa (NIH/CIPRA)	Open-label randomised trial of early (immediate) vs. deferred (after completion of the initiation phase) initiation of ART (ddI, 3TC, EFV). ART will be provided within the TB programme in the early arm while patients on the deferred arm will be referred to the HIV clinic	To start in 2006

HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; TB = tuberculosis; AIDS = acquired immunodeficiency syndrome; ddI = didanosine; 3TC = lamivudine; EFV = efavirenz; NVP = nevirapine; PART = Punctuated Anti-Retroviral Treatment; NIAID = National Institute of Allergy and Infectious Diseases; ARV = antiretroviral; ABC = abacavir; ZDV = zidovudine; ART = antiretroviral treatment; EDCTP = European and Developing Countries Clinical Trial Partnership; TDR = Special Programme for Research and Training in Tropical Diseases; SCC = short-course chemotherapy; NNRTI = non-nucleoside reverse transcriptase inhibitor; WHO = World Health Organization; ANRS = Agence Nationale de Recherches sur le Sida; NIH = National Institutes for Health; CIPRA = Comprehensive International Program of Research on AIDS.

- New persistent fevers without an identifiable source or reason (e.g., an allergic reaction, malaria) and/or worsening or emergence of dyspnoea, and/or stridor, and/or increase in lymph node size, and/or development of abscesses, and/or development of abdominal pain with ultrasound evidence of abdominal adenopathies and/or unexplained CNS symptoms.
- Adequate adherence to ART and TB treatment.*

Such a diagnosis can be made at all health care levels.

ii A confirmed TB IRIS case can be defined as a patient who meets the following three criteria:

- Radiological examinations showing worsening or emergence of intra-thoracic lymphadenopathy, pulmonary infiltrates, pleural effusions, abdominal lymph nodes, hepatosplenomegaly
- A good virological response* and/or an increased CD4+ lymphocyte count,* and/or conversion of TST from negative to positive and/or adequate adherence to ART and TB treatment.
- A clear exclusion of other conditions that could explain the clinical manifestations of the patient, such as TB treatment failure or other concomitant infections, tumours or allergic reactions.

2 Unapparent TB at the start of HAART ('unmasking' type of TB IRIS).† Before the start of HAART there were insufficient clinical symptoms/signs to justify the start of TB treatment; chest X-ray (CXR) was normal and in patients presenting with cough at least three sputum smears were negative for AFB.

Patients should have the following characteristics:

i Good virological response* and/or an increased CD4+ lymphocyte count* and/or conversion of TST from negative to positive and/or adequate adherence to ART.
ii TB appeared within the first 6 months of starting HAART
iii Formation of abscesses and/or symptomatic enlarged mediastinal and/or abdominal lymph nodes and/or pulmonary infiltrates develop within <2 weeks.

RECOMMENDATIONS FOR THE TREATMENT OF HIV-POSITIVE PATIENTS WITH ACTIVE TB IN SETTINGS WHERE HAART IS AVAILABLE

1 Exclude active TB before starting HAART. Programmes that provide HAART should increase their

* The degree of virological or immunological response or adherence needed will have to be established in prospective studies.

† Some of the latter patients may simply be patients in whom the diagnosis of active TB was missed at the start of HAART and who later progressed towards overt TB due to lack of treatment.

capacities to diagnose TB. This should include reliable sputum smear examination at the primary health care level. At the secondary level, this can include performing CXR in persons with weight loss and fever of unknown origin, even in the absence of cough, and, in the presence of unexplained abdominal pain, fever or weight loss, an abdominal ultrasound to detect abdominal lymph nodes. The usefulness of CXR in the screening process for starting TB prophylaxis has been questioned,[49] but should be re-evaluated when screening is performed for TB in very sick patients with $CD4^+$ lymphocyte counts <200 cells/μl. A recent study in Tanzania showed that clinical and subclinical TB only detectable by sputum culture was present in 7% of ambulatory HIV-infected persons.[50] Therefore, performing mycobacterial cultures should be considered at the tertiary level.

2 In case a patient needs HAART but also has TB, TB treatment should be given priority. There are pros and cons to guide the decision on when best to start HAART in TB patients. High case fatality rates in HIV-positive patients with active TB have been reported (up to 40%), especially in the first 2 months of TB treatment.[51] Interventions such as intensified case finding and cotrimoxazole prophylaxis are important interventions to reduce the case fatality rate. Early HAART may also be able to reduce the case fatality rate. Although early initiation of HAART may potentially cause more TB IRIS events, these events seem rarely to be fatal. In patients with CD4 cell counts <200/μl or World Health Organization (WHO) stage 4, ART should be initiated between 2 weeks and 2 months after the start of TB treatment, when the patient has stabilised on TB treatment. Delaying the start of HAART for even longer, until the TB treatment continuation phase, could be considered in case there is no access to efavirenz (EFV) or rifabutin and for patients with a CD4 cell count between 200 and 350/μl.

3 Health care workers involved in ART programmes in countries where TB is highly prevalent should be trained to diagnose and manage TB IRIS patients.

4 Once TB IRIS develops, it is probably advisable to continue HAART, unless the TB IRIS is life-threatening. In patients treated with a rifampicin (RMP) containing TB regimen, a switch from a nevirapine (NVP) to an EFV-based regimen will often be necessary. The high incidence of TB IRIS after HAART has made certain programmes decide to switch their first-line regimen from an NVP- to an EFV-containing regimen (ensuring effective contraception for women of child-bearing age). For the same reason, a switch from a stavudine (D4T) to a zidovudine (ZDV) containing regimen could be considered (to prevent the development of polyneuritis in patients who may require concomitant isoniazid [INH] treatment). In case of life-threatening TB IRIS in patients taking a fixed-dose combination including NVP, the NVP should be stopped first and the two nucleoside analogues should be continued for about 7 days.[52] TB treatment should be continued, and adding prednisolone or NSAIDs may be beneficial.

CONCLUSION

We propose a clinical case definition of TB IRIS that could be used in resource-constrained settings. Such a case definition could be used to determine the incidence and potentially associated long-term morbidity and mortality of TB IRIS. This information is important for the planning of clinical trials that are needed to answer questions on how this phenomenon could be prevented and treated.

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RÉSUMÉ

L'infection par *Mycobacterium tuberculosis* représente probablement un tiers des événements du type syndrome inflammatoire de reconstitution immunitaire (IRIS) lié au virus de l'immunodéficience humaine (VIH), particulièrement dans les pays en développement où les co-infections par le VIH et la tuberculose (TB) sont très courantes. De petites études de cohortes de patients séropositifs pour le VIH et atteints d'une TB active, soignés par un traitement antirétroviral (ART), suggèrent une incidence de TB IRIS variant entre 11% et 45%. Les facteurs de risque de TB IRIS suggérés dans certaines études mais pas dans d'autres comportent : une mise en route de l'ART dans les 6 semaines du début du traitement de la TB, une maladie extrapulmonaire ou disséminée, un décompte faible de lymphocytes CD4, une charge virale importante au début de l'ART, et une bonne réponse immunologique et virologique au cours du «highly active antiretroviral therapy» (HAART). Il est important de se mettre d'accord sur une définition clinique des cas de TB IRIS qui pourrait être utilisée dans les contextes à ressources limitées. Une telle définition des cas devrait être utilisée pour déterminer l'incidence exacte ainsi que les conséquences de l'IRIS TB et pourrait être très utile dans les essais cliniques qui sont nécessaires pour répondre aux questions concernant la prévention et le traitement de ce phénomène.

RESUMEN

La infección por *Mycobacterium tuberculosis* corresponde a un tercio de los casos del síndrome de reconstitución inmunitaria inflamatoria (IRIS) asociado con la infección por el virus de la inmunodeficiencia humana (VIH), en particular en los países en vías de desarrollo donde la coinfección por VIH y tuberculosis (TB) es muy frecuente. Pequeños estudios de cohortes de pacientes con serología positiva para el VIH y TB activa en curso de tratamiento antirretrovírico (ART) indican que la incidencia de la asociación de TB y IRIS oscila entre el 11% y el 45%. Se han propuesto factores de riesgo para la asociación en algunos artículos, pero no todos los estudios los han confirmado ; entre ellos se cuentan el comienzo del ART durante los primeros 6 meses del tratamiento antituberculoso, la TB extrapulmonar o diseminada, una recuento bajo de linfocitos CD4 y por último, una viremia alta al comienzo del tratamiento antirretrovírico de gran actividad (HAART), con una buena respuesta inmunitaria y vírica al mismo. Es importante llegar a un acuerdo sobre una definición de caso clínico de IRIS y TB que pueda utilizarse en medios con recursos limitados. Tal definición podría servir para determinar la incidencia y las consecuencias de esta asociación y sería de gran utilidad en los ensayos clínicos necesarios con el objeto de resolver los interrogantes que persisten sobre la prevención y el tratamiento del fenómeno.